AR 2 4 1990

J 24.2: C 52

Clandestinely Produced Drugs, Analogues and Precursors

Problems and Solutions

Proceedings of an international conference on assessment of drug control issues of controlled substance analogues, co-sponsored by the World Health Organization and the Drug Enforcement Administration (United States of America), in Rabat, Morocco, 8-11 September 1987.

Clandestinely Produced Drugs, Analogues and Precursors

Problems and Solutions

I

BLANK PAGE

Clandestinely Produced Drugs, Analogues and Precursors

Problems and Solutions

— Editors —

M. Klein, F. Sapienza, H. McClain, Jr.
Drug Enforcement Administration
Office of Diversion Control, Drug Control Section
Washington, D.C., United States of America

I. Khan
World Health Organization
Psychotropic and Narcotic Drugs Unit
Division of Drug Management and Policies
Geneva, Switzerland

Proceedings of an international conference on assessment of drug control issues of controlled substance analogues, co-sponsored by the World Health Organization and the Drug Enforcement Administration (United States of America), in Rabat, Morocco, 8-11 September 1987.

United States Department of Justice
Drug Enforcement Administration
Washington, D.C.
1989

U.S. Department of Justice
Drug Enforcement Administration

As the largest law firm in the Nation, the Department of Justice serves as counsel for its citizens. It represents them in enforcing the law in the public interest. Through its thousands of lawyers, investigators, and agents, the Department plays the key role in protection against criminals and subversion, in ensuring healthy competition of business in our free enterprise system, in safeguarding the consumer, and in enforcing drug, immigration, and naturalization laws. The Department also plays a significant role in protecting citizens through its efforts for effective law enforcement, crime prevention, crime detection, and prosecution and rehabilitation of offenders.

Moreover, the Department conducts all suits in the Supreme Court in which the United States is concerned. It represents the Government in legal matters generally, rendering legal advice and opinions, upon request, to the President and to the heads of the executive departments. The Attorney General supervises and directs these activities, as well as those of the U.S. attorneys and U.S. marshals in the various judicial districts around the country.

Preface

Drug abuse continues to be on the increase and remains a great challenge to humanity. The evolutionary programme of the World Health Organization to provide health for all by the year 2000 can only become a reality through concerted efforts to accomplish this objective with the cooperation of the Member States, their organizations and dedicated professionals.

There are already many substances, natural and synthetic, e.g., heroin, amphetamine, cocaine, and LSD, which are made available for abuse by unscrupulous and criminal individuals and organizations. The appearance of controlled substance analogues (designer drugs) has added a new dimension to the problems associated with the use and abuse of narcotic drugs and psychotropic substances.

I am confident that the Proceedings of this international meeting, cosponsored by the Drug Enforcement Administration of the United States of America and the World Health Organization, will prove invaluable in drawing attention to this serious public health problem.

H. Nakajima, M.D., Ph.D.
Director-General
World Health Organization

Acknowledgment

The participants gratefully acknowledge the partial financial support towards this meeting by the United Nations Fund for Drug Abuse Control and to its Executive Director, Dr. Guiseppe di Gennaro who personally came to Rabat and participated in the meeting, to His Excellency Taieb Bencheikh, Minister of Health of the Kingdom of Morocco, for providing technical assistance, to the Honorable Thomas A. Nassif, United States Ambassador to Morocco, and his staff who provided facilities and administrative support, and to Dr. Edward C. Tocus, Chief of the Drug Abuse Staff of the U.S. Food and Drug Administration, for his work in consulting with WHO and DEA regarding this meeting but could not participate because of illness.

Contents

Preface v

Acknowledgment vi

List of Participants ix

Introduction xiii

Recommendations and Proposals xvii

Welcoming Remarks of His Excellency Taieb Bencheikh xix
Minister of Health of the Kingdom of Morocco

Welcoming Remarks of the Honorable Thomas Nassif xxi
U.S. Ambassador to Morocco

Statement of Mr. Giuseppe di Gennaro xxiii
Assistant-Secretary General, Executive Director of the United Nations Fund for Drug Abuse Control

Closing Remarks by Dr. Mustapha Akhmisse xxvii
Secretary General, Ministry of Public Health, Kingdom of Morocco

- International Concerns and Aspects of the Problems -

Address on Behalf of the World Health Organization 1
Dr. Inayat Khan

The Evolution of Designer Drugs 3
Gene R. Haislip

Designer Drugs: The California Experience 7
Gary L. Henderson, Ph.D.

Statistics and Trafficking Patterns of Drugs and Chemicals 21
Terrance W. Woodworth and Ian Bain

The Activities of the Laboratory of the United Nations Division of Narcotic Drugs in Supporting International Drug Control 29
Cherif M. Kouidri, Ph.D.

- Production of Controlled Substances and Analogues -

Synthesis and Evaluation of Amphetamine Analogues 39
Richard A. Glennon, Ph.D.

4-Phenylpiperidine Analgesics, Fentanyl and Fentanyl Analogues—Methods of Synthesis 67
F. Ivy Carroll, Ph.D. and George A. Brine, Ph.D.

Illicit Synthesis of Phencyclidine (PCP), Lysergic Acid Diethylamide (LSD), Methaqualone and Their Analogues 91
Dr. A.W. Scaplehorn

Clandestine Production Processes for Cocaine and Heroin 95
Donald A. Cooper

- Structure-Activity Relationships and Pharmacology -

Stimulants and Hallucinogens: Structure and Stereostructure-Activity Relationships 117
Pedro A. Lehmann F., Ph.D.

Structure-Activity Relationships of Morphinomimetics 125
J.P. Tollenaere, Ph.D.

Preclinical Pharmacology of Drug Abuse 135
K. Kelemen, M.D., D.Sc.

Clinical Pharmacology and Designer Drugs 147
Jordi Cami, M.D.

Assessment of Abuse Liability and Harm Liability of Drugs of Abuse 161
Tomoji Yanagita, M.D., Ph.D.

- Public Health Risks -

Public Health Risks Resulting from Processing Impurities in Clandestine Drugs 175
Michael Klein, Ph.D.

The Methylenedioxy Amphetamines: Pharmacological, Behavioral and Neurotoxic Effects 195
Kevin T. Finnegan, M.D., Ph.D., and Charles R. Schuster, Ph.D.

Organ Toxicity 207
S.D. Ferrara, M.D. and L. Cima

Behavioral Toxicity of Phencyclidine 233
Paul Luisada, M.D.

- Detection, Identification and Epidemiology -

Developing Indicators of Illicit Use of Analogues and Similar Abuse Patterns 239
Prof. Dr. med. Wolfram Keup

Thailand Data Base on Drug Dependence and Illicit Drugs: An Appraisal of Merit for Problem Monitoring and Intervention Planning for Demand Reduction 257
Vichai Poshyachinda, M.D.

Concern of Developing Countries in Illicit Manufacture of Controlled Substances and their Analogues 273
Dr. F.R. Yousuf Fazli

The Abuse of Illicit Substances in Greece 283
Dr. Meni Malliori

- Legislation, Law Enforcement and Legal Problems -

Investigative Techniques of Controlled Substance Cases 285
Raymond J. McKinnon

U.S. Analogue and Chemical Legislation 291
Gene R. Haislip

Misuse of Drugs Enforcement in the United Kingdom 295
Dr. A.W. Scaplehorn

Drug Law Enforcement in a Developing Country 301
Prof. Juan Carlos Garcia Fernandez

Concerns of Industry 317
Margaret Cone

The Problem of Analogues vs International Drug Treaties 319
Dr. Istvan Bayer

Author Index 323

Subject Index 325

List of Participants

1. *Mr Edward A. Babayan, President of the Permanent Committee on Narcotic Drugs of the USSR, Head of the Department of Ministry of Health, Rochmanovski, Pereulok 3/5, 101 451 *Moscow*, USSR

2. Dr István Bayer, International Manager, National Institute of Pharmacy, H-1051, *Budapest*, Zrinyl U.3., Hungary

3. Professor C. M. H. Belkahia, Department of Pharmacology, Faculty of Medicine—Tunis, 9-rue PR Zouheir Essafi, *Tunis*, Tunisia (WHO Temporary Adviser)

4. Dr Jean-Pierre Bertschinger, Head of Division of Pharmacy and Narcotic Drugs, Federal Office of Public Health, Falkenplatz 11, 3001 *Bern*, Switzerland

5. Dr Richard S. Burns, Vanderbilt University Medical Center, Department of Psychiatry, A-2215 Medical Center North, *Nashville*, Tennessee 37232, United States of America

6. Mr Helmut Butke, Counsellor, Federal Ministry for Youth, Family, Women and Health, 5300 *Bonn* 2, Federal Republic of Germany

7. Dr Jordi Camí, Director, Institut Municipal d'Investigacio Medica, P. Maritim 25-29, 08003 *Barcelona*, Spain

8. Dr F. I. Carroll, Director for Organic/Medical Chemistry, Research Triangle Institute, Chemistry and Life Sciences, P.O. Box 12194, *Research Triangle Park*, North Carolina 27709-2194, United States of America

9. *Dr Tayeb Chkilli, Dean of Medical Faculty, Medical School of Rabat, *Rabat*, Morocco

10. Mr Donald Cooper, Senior Forensic Chemist, Special Testing and Research Laboratory, Drug Enforcement Administration, *McLean*, Virginia 22102-3494, United States of America

11. Dr Philip O. Emafo, Director, Pharmaceutical Services, Federal Ministry of Health, Federal Secretariat Complex II, Ikoyi, *Lagos*, Nigeria (WHO Temporary Adviser)

12. Dr F. R. Yousuf Fazli, Director, Central Drugs Laboratory, Ministry of Health, *Karachi*, Pakistan (WHO Temporary Adviser)

13. Professor Juan Carlos Garcia Fernandez, Representante titular de la Universidad de Buenos Aires, Facultad de Farmacia y Bioquimica, Junin 760, *Buenos Aires*, Argentina

14. Dr S. David Ferrara, Director, Laboratory of Clinical and Forensic Sciences, University of Padova, Via Falloppio 50, 35100 *Padova*, Italy (WHO Temporary Adviser)

15. Dr Kevin Finnegan, Institute for Medical Research, 2260 Clove Drive, *San Jose*, California 95128, United States of America

16. * Mr Tony Francfort, Chef de Bureau des Stupéfiantes, Direction de la Pharmacie et du Médicament, Ministère des Affaires Sociales et de la Solidarité Nationale, 1 Place Fontenay, 75007 *Paris*, France

17. Dr Susan George, Department of Pharmacology, Faculty of Medicine, University of Toronto, Medical Science Building, 1 Kings College Circle, *Toronto*, Ontario M5S 2S1, Canada

18. *Brig. Gen. Youssef Gharaiba, Council of Arab Ministers of Interior, P.O. Box 490, *Tunis*, Tunisia

19. Dr Richard A. Glennon, Professor of Medicinal Chemistry, Medical College of Virginia, Virginia Commonwealth University, P.O. Box 581, MCV Station, *Richmond*, Virginia 23298-0001, United States of America

---

*Invited but unable to attend.

20. Mr John W. Gunn, Deputy Assistant Administrator, Office of Science and Technology, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America

21. Mr Gene R. Haislip, Deputy Assistant Administator, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America (Chairman)

22. Dr Gary Henderson, Associate Professor of Pharmacology and Environmental Toxicology, School of Medicine, University of California, *Davis*, California 95616, United States of America

23. Dr Juhana Idänpään Heikkilä, Chief Medical Officer for Pharmacology, National Board of Health, Siltasaarenkatu 18A, 00530 *Helsinki*, Finland

24. *Dr R. D. Hossie, Chief, International Control and Licensing Division, Bureau of Dnagerous Drugs, Health Protection Branch, *Ottawa* K1A OL2, Ontario, Canada

25. Mr Lars Hulstrand, Assistant Under-Secretary, Ministry of Health and Social Affairs, *Stockholm*, Sweden

26. Professor K. Kelemen, Semmelweis University of Medicine, Department of Pharmacology, *Budapest*, Nagyvarad ter 4. P.O.B. 370, Hungary 1445 (WHO Temporary Adviser)

27. Professor Dr Med. W. Keup, Jos.-Schauer-Str. 16, 8039 *Puchheim*, Federal Republic of Germany

28. Dr Inayat Khan, Senior Medical Officer, PND, World Health Organization, 1211 *Geneve* 27, Switzerland (Secretary)

29. Dr Michael Klein, Drug Control Section, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America (Co-Rapporteur)

30. Dr Pedro A. Lehmann, Professor Titular, Centro De Investigación De Estudios Avanzados Del IPN, Departmento de Farmacologia y Toxicologia, Apartado Postal 14–740, Mexico, D.F., C.P. 07000

31. Dr Chen Chan Ling, National Institute for Control of Pharmaceuticals and Biological Products, *Beijing*, People's Republic of China (WHO Temporary Adviser)

32. Dr Paul V. Luisada, Director, Northern Virginia Institute of Psychiatry, 5537 Hempstead Way, *Springfield*, Virginia 22151, United States of America

33. Dr Meni Malliori, Special Adviser in the Ministry of Health-Welfare and Social Security, 27 Parthenonus Street, 11742 *Athens*, Greece (WHO Temporary Adviser)

34. Mr Howard McClain, Jr., Chief, Drug Control Section, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America

35. Mr Raymond J. McKinnon, Chief, Dangerous Drugs Investigations Section, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America

36. Dr Paes Mehdi, Professor of Psychiatry, University of Rabat Medical School, *Rabat*, Morocco (WHO Temporary Adviser)

37. Associate Professor Vichai Poshychinda, Chief of Drug Dependence Research Centre, Institute of Health Research, Chulalongkorn University, *Bangkok* 10500, Thailand (WHO Temporary Adviser)

38. Mr Neil Pouliot, Inspector, Officer-In-Charge, National and International Drug Operations, Royal Canadian Mounted Police, 1200 Alta Vista Drive, *Ottawa*, Canada K1A OR3

39. Professor Bror Rexed, Meritullinkatu 20 A 10, 00170 *Helsinki*, Finland

40. Mr Frank Sapienza, Drug Control Section, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537,

---

*Invited but unable to attend.

United States of America (Co-Rapporteur)

41. Dr A. W. Scaplehorn, Director, Forensic Science Laboratory, Home Office, Priory House, Gooch Street North, *Birmingham* B5 6QQ, United Kingdom (WHO Temporary Adviser)

42. *Dr Charles R. Schuster, Director, National Institute on Drug Abuse, 5600 Fishers Lane, *Rockville*, Maryland 20857, United States of America

43. Mr Ali Sedrati, Director, Service Centrale de la Pharmacie, Ministère de la Santé Publique, 335 Ave Mohammed V, *Rabat*, Morocco (WHO Temporary Adviser)

44. Mr P. G. Spurgeon, Home Office, Queen Anne's Gate, *London* SW1 H9AT, United Kingdom

45. *Dr G. Tadesse, Vice Minister of Health, P.O. Box 1234, *Addis Ababa*, Ethiopia (WHO Temporary Adviser)

46. Mr Michael Thomas, Referatsleiter, Bundeskriminalamt, Thaerstr. 11, 6200 *Wiesbaden*, Federal Republic of Germany

47. *Dr Edward C. Tocus, Food and Drug Administration, 5600 Fishers Lane, *Rockville*, Maryland 20857, United States of America

48. Dr Jan Tollenaere, Janssen Pharmaceutica, Department of Theoretical Medicinal Chemistry, Turnhoutsebaan 30, B-2340 *Beerse*, Belgium

49. Dr Tomoji Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, 1433 Nogawa, Myamae-ku, *Kawasaki* 213, Japan (WHO Temporary Adviser)

Representatives of Other Organizations

United Nations Division of Narcotic Drugs

Dr Cherif Kouidri, Applied Scientific and Technical Information Section, UN/DND, P.O. Box 500, 1400 *Vienna*, Austria

International Narcotics Control Board

Dr A. S. Elmi (Member—INCB), Department of Pharmacology and Traditional Medicine, Faculty of Medicine, Somali National University, *Mogadishu*, Somalia (WHO Temporary Adviser)

International Criminal Police Organization—Interpol

Mr Ian Bain, International Criminal Police Organization, 26 rue Armengaud, 92210 *Saint Cloud*, France

Mr Terrance Woodworth, International Criminal Police Organization, 26 rue Armengaud, 92210 *Saint Cloud*, France

United Nations Fund for Drug Abuse Control

Mr Giuseppe di Gennaro, Assistant Secretary General, Executive Director, UNFDAC, Vienna International Centre, P.O. Box 500, 1400 *Vienna*, Austria

Mr William O'Hara, UNFDAC, Vienna International Centre, P.O. Box 500, 1400 *Vienna*, Austria

Permanent Secretariat of the South American Agreement on Narcotic Drugs and Psychotropic Substances

Mr Robert Punte, Combate de los Pozos 2133 1er. piso, 1245 *Buenos Aires*, Argentina

---

*Invited but unable to attend.

International Federation of Pharmaceutical Manufacturers Associations

Ms Margaret Cone, Vice President for Scientific Affairs, IFPMA, 67 rue de Saint-Jean, 1201 *Geneva,* Switzerland

Observers

Dr Martha Harkey, Department of Pharmacology, School of Medicine, University of California, *Davis,* California 95616, United States of America

Mr Arnold Schifferdecker, Political Counselor and Acting Narcotics Coordinator, United States Embassy, *Rabat,* Morocco

Support Personnel

Ms Carole A. Whalen, Administrative Officer, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America

Ms Lina Gutierrez, Secretary, Office of Diversion Control, Drug Enforcement Administration, 1405 I Street N.W., *Washington, D.C.* 20537, United States of America

Introduction

During the past two decades, the demand for psychoactive substances has led to the growing problem of illicit clandestine laboratories. These laboratories have proliferated because of the ease of production, the often minimal skills needed for their operation and large profits which can be produced. Equipment, chemicals, and facilities are relatively easy and inexpensive to obtain. Operators have included students, teachers, chemists and engineers who have utilized university, government or industrial laboratories for the illicit production of psychoactive substances. The majority of clandestine laboratories are established in houses, garages, backyard sheds, or apartments and have relatively modest production capabilities. Large-scale laboratories have been set up in rented warehouses or other large buildings.

The manufacture, trafficking, and abuse of clandestinely produced drugs is a worldwide problem. International trafficking in the precursor chemicals, solvents, reagents and catalysts often proceeds under the guise of legitimate commerce. Frequently, the chemicals are shipped from one nation to another where they are used for clandestine production of illicit drugs which are returned to the original chemical source nation for sale on the illicit market. Other third-party nations have also become the marketplace for the products of clandestine laboratories. Clandestine laboratories have produced the stimulants amphetamine, methamphetamine, and cocaine, the depressants methaqualone and mecloqualone, the narcotic drugs heroin and variants of fentanyl, and a wide variety of hallucinogenic drugs including phencyclidine (PCP), lysergide (LSD), and 3,4-methylenedioxyamphetamine (MDA).

In recent years, chemists in clandestine laboratories have synthesized substances which produce the pharmacologic effects of controlled substances but which are slightly different chemically and thus are not subject to the provisions of national or international precepts. These chemical variants (or analogues) have consisted of variations of the parent compounds fentanyl, meperidine (pethidine), and the hallucinogenic amphetamine derivatives. By selling the analogues, the clandestine manufacturer profits from the distribution of dangerous abusable substances while avoiding the penalties levied against those illegally trafficking in controlled substances. A novel and dangerous aspect of the current phenomenon is its application to the clandestine production of highly potent synthetic narcotic substances.

The World Health Organization (WHO) is an international health coordinating body which participates very actively within the United Nations system leading to the rational use of narcotic drugs and psychotropic substances with dependence liability. A major task before WHO is to recommend narcotic drugs or psychotropic substances for international control. WHO has set up guidelines for carrying out reviews of those substances which have been approved by its Executive Board and recommended by the UN Commission on Narcotic Drugs (CND).

The WHO Program Planning Working Group which met in March 1986 expressed concern about controlled substance analogues and recommended that WHO review this subject and prepare itself for helping countries face the problem.

WHO participated in the Leadership Conference on Controlled Substance Analogues organized by the U.S. Drug Enforcement Administration (DEA) in San Francisco June 1986. This meeting brought together U.S. based law enforcement and public health officials to discuss the problem. The conference recommendations, although addressed to the United States, are useful guidelines to be followed by others facing this problem.

WHO convened an expert group in August 1986 and reviewed the clinical and pharmacological specifications of substances for control under the international drug control treaties involving designer drugs (MNH/PAD/86.13). The report specifically describes (page 8 para. 7.2) four recommendations which are applicable to the controlled substance analogue problem. The recommendations are as follows:

1. Channels for communications on controlled substance analogues should be encouraged among United Nations Division of Narcotic Drugs (UN/DND) and WHO, as well as INTERPOL, and Member States with necessary and available data.

2. The establishment of an international collection of reference substances should be considered as an extension of the collection of samples of controlled substances maintained by UN/DND. Analytical methodology and supplemental analytical data should be compiled and maintained by UN/DND for distribution to Member States. WHO should maintain pharmacological and public health data on the controlled substance analogues for distribution to Member States.

3. The group further suggested that Member States should be alerted to problems caused by controlled substances analogues. They should be made aware of the ability of WHO and UN/DND to help them by providing pharmacological, public health, and chemical information. This group encouraged the exchange of information regarding this problem among Member States through national and international meetings.

4. The group suggested as well that the normal scheduling procedures should be applied to controlled substance analogues where individual substances are involved in international traffic. Amendments to the Conventions to encompass emergency control measures may be considered if a sufficiently grave situation exists and significant international traffic is observed.

The 24th Expert Committee on Drug Dependence which met in April 1987 reviewed the Critical Review document which contained all available information on designer drugs. They decided that there was sufficient data regarding five of these substances to recommend their control under the 1961 Single Convention in Schedules I and IV. Three are fentanyl analogues: (1) alpha-methylfentanyl, (2) acetyl-alpha-methylfentanyl and (3) 3-methylfentanyl and two analogues of meperidine (pethidine): (1) MPPP and (2) PEPAP. These substances were recommended for control by the Director-General of WHO to the Secretary-General of the United Nations. A debate on their control took place before the U.N. Commission on Narcotic Drugs in Vienna in February 1987. The five controlled substance analogues recommended by the WHO for control under Schedule I and IV of the Single Convention on Narcotics, 1961 were so listed in 1988.

Additional assessments of other controlled substance analogues were scheduled for review by the 26th Expert Committee on Drug Dependence in April 1989. An additional six analogues of fentanyl and two analogues of MDA and one analogue of aminorex were to be reviewed.

To focus on the important issues and overall problems regarding the controlled substance analogues, WHO and DEA (USA) organized the Joint Conference on Technical Aspects of Drug Control—*Assessment of Issues Relative to Illicit Substances of Abuse and Controlled Substance Analogues* which was held in Rabat, Morocco, September 8–11, 1987. The conference was co-sponsored by WHO and DEA since both agencies share the same goals of reducing harm to the public health and social welfare from drug abuse. The conference was a forum for bringing together international public health, scientific, legal and law enforcement experts to address the varied aspects of the problem.

Technical issues regarding the clandestine illicit manufacture of abused substances were examined. As part of the overall clandestine laboratory problem, particular emphasis was placed on the phenomenon of the controlled substance analogues, their chemistry and pharmacology and the risks they present to the public health. Problems regarding the illicit manufacture and distribution of the substances were discussed with a view toward developing remedies at the national and international levels.

The chemicals and precursors used in the illicit synthesis of drugs, their properties, availability and ease of substitution were also examined. The effectiveness of current laws and treaties in dealing with the problem were considered. A threat assessment of potential new abusable substances from clandestine laboratories was addressed by review of chemical processes, structure activity relationships, and the pharmacology and toxicology of already abused substances. Special considerations of developing countries, researchers, consumers and industry were considered as well.

The following papers represent the proceedings of the Joint Conference, the written contributions of the experts, and a summary of the recommendations of the paticipants. The papers are compiled in six chapters which cover the technical aspects of the problem and include a general description of the issues, chemistry, pharmacology, public health risks, detection and identification and legal and law enforcement concerns.

The Editors

BLANK PAGE

Recommendations and Proposals

1. Recognizing that a clear and urgent requirement for an early warning system needs to be established under international arrangements, a draft resolution should be prepared by the Commission on Narcotic Drugs (CND) for adoption by the Economic and Social Council to cover the following matters:

a. to draw attention to the development of illicit controlled substance analogue manufacture at the international level;

b. to establish an early warning system, coordinated by the United Nations whereby the competent national authorities would be informed quickly of the emergence of new analogues (and the relevant chemical/toxicological data);

c. to adopt national legal measures against the unauthorized manufacture, distribution and supply of controlled psychoactive substances/narcotic drugs, psychotropic substances, and their analogues.

2. When a country has evidence of the emergence of a new controlled substance analogue, it should be considered for international control and the United Nations Secretary-General should be notified in conformity with Article 3(1) of the 1961 Convention or Article 2(1) of the 1971 Convention.

3. An emergency scheduling procedure by the United Nations with provisions, for example, for temporary scheduling pending further review should be explored. The procedure should provide for adequate technical consultation in order to ensure that any legitimate research into such compounds is not adversely affected.

4. Countries should establish programs with their industries and commercial enterprises to ensure adequate surveillance of exports and imports of immediate precursors and essential chemicals, and the means to intervene where necesssary upon suspicion within the country or in cooperation with the authorities of other countries about particular consignments.

5. A central information system on drug abuse problems at the international level should be established in an organization such as the World Health Organization (WHO), the United Nations Division of Narcotic Drugs (UN/DND), or Interpol. The central system should maintain an information bank covering problem identification and intervention programs in operation. Each country should establish a corresponding system to serve as information bank and clearing-house if possible.

6. The international organization which becomes responsible for the central information system should seek the voluntary participation of a group of Member States in launching a pilot study. The international organization should encourage another group of countries that share common problems to develop a joint system for sharing drug abuse in-

formation so that this small system can then be expanded on a worldwide basis. The international organization should conduct a survey of existing drug abuse information systems within countries so that the international data base which will subsequently be established can use existing data sources and systems to the maximum extent possible. After worldwide information systems have been surveyed, a uniform standardized reporting format should be adopted to enable intra-system exchange of information. Standards for the quality of the information should also be established by the international body.

7. In relation to recommendation 1(b), above, the WHO and UN/DND should prepare and distribute to health authorities of Member States a manual of information reflecting the current state of knowledge on controlled substance analogues which must be updated regularly. WHO should be the lead agency in the preparation of information on chemical, biological and public health aspects; and UN/DND should be the lead agency for chemical analysis aspects. The establishment of an international collection of reference substances of analogues should be considered as an extension of the collection of samples of controlled substances currently maintained by UN/DND. In the preparation of the manual, advantage should be taken of the specialized knowledge and experience of those national agencies with relevant experience in the problem.

The manual should provide, as far as possible, the following information on each substance:

—chemical nomenclature and structure;

—physico-chemical characteristics;

—major pharmacological and toxicological effects observed in animals with particular reference to acute toxicity studies;

—pharmacokinetics (relevant to sample taking);

—clinical signs and symptoms;

—management and treatment of the patient;

—autopsy findings;

—analytical techniques for chemical identification and assay.

Welcoming Remarks of His Excellency Taieb Bencheikh

Minister of Health of the Kingdom of Morocco

I would like to welcome the participants of this joint conference and congratulate the World Health Organization and the U.S. Drug Enforcement Administration for selecting Morocco as the site for the meeting.

This joint conference will deal with the technical aspects of drug control and its purpose is twofold:

—To identify clandestinely and illicitly manufactured drugs and assess the extent of their abuse.

—To place particular emphasis on analogues of controlled substances, their chemical and pharmacological properties, and their risks to the public health.

The qualifications of the participants is exemplified by their expertise in areas of drug control, commerce, science, and drug manufacturing. I know that they face a very difficult task; each time that experts have succeeded in recognizing the misuse of one or two drugs and then in publicizing this information and in encouraging governments to pass legislation, forces of evil who thrive through drug trafficking begin again with new drugs of abuse. New counter-methods are needed which unfortunately require huge financial resources.

Our task is to never surrender and as it is said in the Koran, our holybook, never does good surrender to evil.

As far as my country is concerned, we support your efforts and we will try, through our representatives, to participate and reinforce them.

We associate ourselves with all the efforts made at the international level in order to thwart drug traffic or abuse.

At a more regional level as well, Morocco is playing a role and is participating actively with its neighbors through agreements which have been signed with the U.S.A., Italy, Spain and the Federal Republic of Germany.

We are currently discussing a master plan with our guest, the Honorable Mr. di Gennaro, Executive Director of the United Nations Fund for Drug Abuse Control (UNFDAC). I would like to take this opportunity to thank him personally for the remarkable efforts that he is making on the international level for a better understanding of the drug problem and better ways to tackle the problem.

Thank you again for having chosen Morocco to hold this conference. I wish you an enjoyable stay in our country and I'm convinced that considering the competence of the eminent persons present this conference will be successful and will help to carry out the struggle against drug abuse.

Welcoming Remarks of the Honorable Thomas Nassif

U.S. Ambassador to Morocco

It gives me great pleasure, on behalf of my Government which is co-sponsoring this conference, and the American Embassy in Rabat, to welcome you to this important gathering of experts.

I will make no pretensions of special knowledge or expertise in the subject you will be examining during the next four days.

However, the major problems you will be addressing, the clandestine manufacture, trafficking and sale of illicit drugs—so-called "Controlled Substance Analogues" or "Designer Drugs"—is one of the Reagan Administration's primary targets in the war on drugs in the United States.

It is evident, even to a layman, that this has quickly become an international social problem of vast proportions.

It is true, as many persons state, that the social causes which lead to drug abuse, particularly in western countries, stimulate demand for the growing and processing of traditional drugs, as well as the manufacture and illicit sale of "man-made" drugs.

My Government is keenly aware that the demand side of drug abuse requires increased attention, research treatment facilities and the human financial resources to cope with that half of the equation.

The United States is devoting major new resources to drug treatment and reduction of drug demand.

But, we emphatically reject that the abuse of drugs is the sole province of the developed western countries, and that demand reduction alone will solve the problem.

The sad truth is that producer countries all over the world are discovering—frequently too late—that availability of drugs inevitably leads to abuse, and that use of so-called "harmless drugs" frequently leads to abuse of harder drugs.

This conference has been convened in recognition of this simple truth:

That the war on drugs and drug abuse is a common problem of mankind and that common solutions—and a unified commitment—are needed to reduce and one day hopefully eliminate this scourge of our generation.

I thank you for coming to concert your efforts with those of others in the very complex and demanding tasks you have set for yourselves.

And, I look forward to learning that your efforts will have taken us another step closer in controlling substances which threaten the vitality of our youth and sap the spirit of our peoples.

Once again, my sincere welcome on behalf of the Embassy and best wishes for a successful conference.

Statement of Mr. Giuseppe di Gennaro

Assistant-Secretary General, Executive Director of the United Nations Fund for Drug Abuse Control

The theme of this Conference gives the opportunity to restate a basic principle which is sometimes neglected. The distinction between licit and illicit drugs does not reside in the molecular structure or the composition of the substance. Each substance can be licit or illicit according to its destination and the procedures followed for its production, commercialization and consumption.

The dichotomy between the two categories of licit and illicit drugs is determined by the legislator. It is the law, in fact, which regards some consumable substances liable for abuse and therefore establishes a system of control for suppressing either their availability or for limiting it to particular cases and circumstances. This means that a drug becomes illicit when in any part of the chain from the production to the consumption, there is a violation of the legal provisions ruling the legal system of control. The legal provisions providing for drug abuse control can have an international or national validity. Corresponding to this there are two legal control systems: an international and a national one. Between the two systems there can be coincidence in substance and in scope. But the national controls can be wider and more severe, for the international law creates a minimum obligation for the States which adhere to it leaving them free to enact additional provisions for making their internal system more efficient.

From your agenda it appears that you are going to consider the element of "clandestinity" as one of the aspects worthy of attention.

And in fact "clandestinity" is a frequent attribute of the activities related to the various aspects of drug abuse and its day by day relevance for the problems posed to detection and identification is out of question.

However, "clandestinity" is not an inherent quality of drug abuse behavior considering that there are instances in which production, trafficking and misuse are made openly. These are the most serious cases because they occur in countries or regions where law enforcement structure is completely absent or ineffective. We know that there are places in which drug traffickers do not even try to shade their illegal business; they act before the eyes of the surrounding community intimidating those few who would like to oppose their activities. I am sure that these grave situations will receive your attention.

This Conference will focus predominantly on those synthetic chemical drugs which are referred to internationally as psychotropic and narcotic substances. They pose many serious problems because of the extension of their abuse and the toxicity of many of them. There are developed industrialized countries which are heavily and mainly affected by these kind of drugs. Psychotropic and narcotic substances also appear to present a tremendous threat to many developing countries as seems to be the case of the African continent.

The illicit trade in psychotropic and narcotic drugs presents characteristics which are peculiar to it. One distinct element resides in the fact that the organizers do not always belong to the normal ranks of criminality, they are disguised as businessmen and therefore defined by criminologists as "white collar" criminals.

The circulation of illicit psychotropic and narcotic substances is sometimes fostered by commercial entities which operate alongside the chain of distribution. In various ways medicines are diverted from the normal channels and are therefore subtracted from the legal controls under which they should remain.

The responsibility of these wrongdoers is very high, because they present, in certain respects, a higher risk for society. In fact, they belong to the category of the so-called "opportunist criminals." This means that they take advantage of the opportunity offered to them by the professional activity, which they are authorized to exercise for the benefit of the society, violating the trust that the community has bestowed on them. There have been and there are cases in which these criminal barons have flooded entire continents with enormous quantities of illicit chemical substances. In this particular sector the law enforcement agencies are confronted with the need to develop a special skill in order to be capable to conduct successful investigations in the context of highly sophisticated procedures. It is the duty of pharmaceutical companies to take appropriate measures to cooperate in preventing psychotropic and narcotic substances from falling into the hands of these unscrupulous criminals.

An important issue in this conference will be that of designer drugs. Very little is known about their production, distribution and consumption. The fact that they can be easily produced everywhere increases our concern for the possible harm to the public health but at the same time can lead us to think that the powerful crime syndicates controlling the international market of illicit drugs may be preoccupied by the spread of designer drugs which poses risks for their monopoly of the illicit drug trade.

How much influence this preoccupation is having on the dynamics of this particular market at present is not exactly known.

The few cognitive elements we have at present bring us to think that designer drugs while a grave social threat are not yet controlled by strong criminal organizations. Anyhow more information is needed to anticipate future developments.

This Conference gives an opportunity to advance the dialogue between experts in the disciplines of health and law enforcement. The United Nations Fund for Drug Abuse Control (UNFDAC) is particularly interested in following your discussions being well aware of the need for a continuous flow of information between these two sectors. In fact, the success of the national and international controls on illicit drug trafficking and abuse is strictly dependent on close collaboration between those who have scientific knowledge on the nature, composition and effects of the substances and those who have experience in the dynamics of the illicit market and related behaviors.

BLANK PAGE

Closing Remarks by Dr. Mustapha Akhmisse

Secretary General, Ministry of Public Health, Kingdom of Morocco

During these past days the Conference participants have been dealing with the means for better control of drugs and their analogues. They have also analyzed their pharmacological, medical and judicial aspects. The quality of the suggestions and recommendations which have emerged from your discussions attest to the seriousness of the issues. I am persuaded that your conclusions will help the international community to better identify those substances and to control their use.

It is an honor for the Kingdom of Morocco to have hosted this Conference and to have profited from the rich experience. Morocco has always considered that the fight against drug abuse can be effective only with international concertation and cooperation, and for this reason it has always associated itself with every national, bilateral and international action in this field.

It has also been with great pleasure during the work of this conference to have received Mr. di Gennaro, Executive Director of the United Nations Fund for Drug Abuse Control and his collaborator Mr. O'Hara with whom it is hoped that Morocco's willingness to cooperate in the fight against drug trafficking will be further confirmed.

I take this opportunity to thank again the WHO and the DEA for all the effort they have always deployed to fight against drug abuse. I thank all of those people who have contributed and participated in this meeting and I wish you a pleasant stay in our country which you can consider your own. In the name of my Minister, I declare this meeting adjourned.

BLANK PAGE

International Concerns and Aspects of the Problems

XXIX

BLANK PAGE

Address on Behalf of the World Health Organization

Dr. Inayat Khan

I bring you greetings from Dr. H. Mahler, Director General of the World Health Organization, who considers this meeting an important landmark in the efforts of people and nations to achieve health for all by the year 2000 as an overriding priority.

Why does this conference represent an important landmark? Every available resource is needed and every individual is important to contribute to the achievement of health for all by the year 2000. Chemicals and, in particular, drugs are an essential part of our lives. However, the wise approach is to choose those which we consider essential or useful and to discard those which have shown repeatedly to be creating more problems than they relieve or cure in some countries. The very useful and essential role of the pharmaceutical industry is ackowledged in these efforts.

There are others who have some knowledge about drugs and through criminal acts offer to society substances which create tremendous problems to public health, thus utilizing the already limited resources available in the health and social welfare section of society.

The manufacture, trafficking and abuse of clandestinely produced drugs has increased dramatically in recent years and have become worldwide problems. Chemists in clandestine laboratories have also begun synthesizing analogues of controlled substances which produce the pharmacologic effects of controlled substances but which, because of slight variations in chemical structure, are not subject to the provisions of national and international controls. The clandestine manufacture of abusable substances including controlled substance analogues ("designer drugs") poses serious threats to the public health and safety as well as problems for scientific, medical, legal and law enforcement communities.

WHO has been advised that priority must be given to review this subject and to start a dialogue between health and law enforcement agencies both at national and international levels. Never has the time been more appropriate than now to start this dialogue and make plans for future action.

The UN Division of Narcotic Drugs and INTERPOL are WHO's partners and they accept a joint responsibility to assist and work with member states. There are a number of tasks which have already been identified, e.g., establishing an international collection of reference substances which could be an extension of the collections of samples of controlled substances maintained by the UN Division of Narcotic Drugs.

Analytical methodologies and supplementary analytical data are being compiled by the UN Division of Narcotic Drugs for distribution to member states. WHO in itself needs to maintain data on pharmacological effects and associated public health problems for dissemination to member states.

The recently formulated Comprehensive Multi-disciplinary Document (CMO) at the International Conference on Drug Abuse and Illicit Trafficking at Vienna in June 1987 emphasized a closer cooperation between law enforcement and health agencies. This conference has been planned specifically to implement those recommendations. The purpose of this meeting is to:

1. identify the clandestinely and illicitly manufactured drugs,
2. assess the public health and safety problems associated with their use,
3. discover ways and means of reducing these problems through discussions by the various disciplines and agencies involved,
4. assign specific responsibilities to the various UN agencies and national organizations,
5. prepare a report and a publication to keep others in this field informed.

Lastly, the World Health Organization and I are grateful to the Drug Enforcement Administration (USA) for carrying the major responsibility to convene this conference, technically, administratively and financially. Also to the UNFDAC and its dynamic Executive Director, Mr. di Gennaro, for his support, and finally to the Government of Morocco and its Minister of Health and his colleagues. I would also like to express my appreciation to Dr. Edward C. Tocus of the U.S. Food and Drug Administration, for his work on the conference agenda. He is not able to participate in this meeting because of illness. We wish him well.

The Evolution of Designer Drugs

Gene R. Haislip

In the early 1980's, United States drug control officials became aware of the development of a new and dangerous problem of drug abuse and illicit traffic. This was the advent of the so-called "designer drugs," powerful and toxic analogues of narcotic and hallucinogenic drugs which were nevertheless outside of the parameters of existing legal controls. Their appearance and spread represented a novel challenge to the diverse official and professional communities responsible for dealing with the drug problem in the areas of law enforcement, treatment, laboratory analysis and research. Some of the compounds were extremely powerful analogues of synthetic narcotics and thousands of times more potent than morphine. Some produced bizarre and unpredictable effects with strong evidence of neurotoxicity. This development has understandably generated alarm within the United States and other countries. The lessons of recent decades support the need for concerned experts and officials to consider the matter urgently so as to prepare the world community for a new threat to public health and safety. Experience has shown that new developments in the drug abuse problem have seldom remained long confined to the country of their origin.

Certain dimensions of the problem, such as those relating to the specific biological activity of particular compounds, can only be determined through lengthy and careful research. Nevertheless, the phenomenon as a whole admits of certain generalities which help elucidate present and future concerns. It is important for this reason that experts and authorities view this development not only in its aspects of novelty and particularity, but also in the social and historical context in which it is occurring. Viewed in this manner, it appears that the clandestine manufacture of controlled substance analogues is but a further development in the latest and most advanced stage of the drug traffic, that of the criminal acquisition of the total means of drug production.

Drug abuse and illicit traffic must be viewed as dynamic phenomena which are part of modern culture establishing itself in every corner of the world. Indeed, they are tailored to, and largely dependent upon, this modern culture of advancing science, technology, and mass production of low cost merchandise. And like so many other aspects of this new condition of society, much of humanity is uneducated and unprepared to cope with it. In this sense, the modern drug problem is conceptually identical to the problem of industrial pollution, and the many other threats from powerful but potentially destructive technologies. A brief review of the historical development of drug traffic and abuse will serve to put the problem in its proper context.

It is sometimes said that drug abuse is nothing new, in fact that it is a human tradition. The same may be said for warfare. But the novelties of the present circumstance are sufficient to cause alarm and incite rigorous action even beyond that which was true of the past. For the greater part of human experience, drug abuse has been confined to isolated cultures, ceremonial circumstances, and crude vegetable preparations of relatively low potency. The only exception is ethyl alcohol which represents a public health disaster of major dimensions. Now it may be said that, increasingly, none of these restraining and mitigating features applies to the modern drug problem. It is at once characterized by the prevalance of extremely potent substances used addictively across social, political, and geographic boundaries and in life circumstances where brief individual impairment can quickly cause harm and destruction. The change which has occurred is in the science and technology with which drugs are discovered, manufacured, advertised, and marketed. The rapidly accelerating sophistication in these areas continues to compound the dangers of the situation.

For many years the refinement of naturally-occurring alkaloids represented the major advancement. This was the period of the nineteenth century and the isolation of morphine from the opium poppy and cocaine from the coca leaf. The process was expensive, commerce slow and the world still lived by many languages and cultural traditions. Drug traffic was still confined to smoking opium. Other problems were caused by overzealous marketing of patent medicines.

The discovery of heroin marked a subtle change. It was a "laboratory drug" of great potency and did not require great sophistication to manufacture. In fact, the illicit heroin laboratory operator is often referred to as a "cook" because he actually proceeds by a traditional "recipe" in his method. Formidable obstacles to the widespread illicit distribution of heroin were presented by the great distances of production areas from the ultimate consumers. The same situation pertained with regard to the refinement and distribution of cocaine.

The next major development affecting the drug problem was the development and establishment of a large "high-tech" pharmaceutical industry based in large part upon the synthesis of highly potent substances of a type and number which had never previously existed. This industry could not only create new compounds but produce them from readily available chemicals in such enormous numbers as to make them available throughout society at modest cost. As a result, all manner of pharmaceuticals are now widely consumed for a great diversity of purposes relating to human need and desire. In addition to those consumed for clear medical need, there are numerous preparations available to induce sleep, energy, weight loss, growth of muscle tissue, etc. A major controversy exists concerning the value and safety of many of these. Market forces, however, often perpetuate patterns of substance consumption which are clearly harmful to the individual and society as is the case of alcohol and tobacco.

Some of the products of this technological break-through had abuse liabilities virtually identical to the natural narcotics and cocaine. Their wide availability, low manufacturing costs, and the lack of legal controls, led to the growth of a large problem of traffic and abuse. For example, in the 1960's, prior to the enactment of the Drug Abuse Control Amendments of 1965, billions of dosage units of amphetamines and barbiturates were manufactured in the United States as compared to the present low level. For example, it is estimated that the manufacturing quota for methamphetamine and amphetamine is now about .005% of what it was in 1969. This represented the third phase of development in the drug problem, the diversion of the products of new scientific synthesis and industrial technologies. It remains a major factor in virtually all countries, including those developing countries which have no industry of their own but are often the unwilling market for others.

The final phase of the instant problem represents but the latest development which began roughly in the early 1960's in California. Here, for the first time, modern scientific and technological capability was applied to the manufacture of drugs of abuse outside of approved channels and exclusively for illicit traffic and abuse. Lysergide (LSD) is the prototypic drug of this innovation, but it was soon followed by others such as 3,4-Methylenedioxyamphetamine (MDA), 4-bromo-2,5-dimethoxyamphetamine (DOB), 4-methyl-2,5-dimethoxyamphetamine (STP), and methamphetamine. It proved that industrial societies such as the United States had reached a level where the means of modern pharmaceutical production and the technical knowledge and skill required, were all readily available to permit manufacture of synthetic psychoactive substances outside of the established industry. In the intervening period, successful legal and law enforcement tools have been developed to deal with these problems on an occasional basis, but for whatever reason, not sufficient to eliminate it as a major source of traffic and abuse.

The advent of the "designer drugs" is the second wave of the phenomenon of clandestine manufacture of synthetic drugs of abuse. LSD, MDA and others would have been called "designer drugs" had they appeared more recently. Nevertheless, there are novel aspects of the present situation which merit attention. The manufacture of controlled substance analogues reflects a new level of sophistication in which we see that illicit activity can duplicate the technical sophistication of the research community manufacturing a seemingly endless variety of analogues. The potency of the new compounds thus made available may not surprise research chemists who have known of such possibilities, but it is a new menace in the streets.

Finally, this development has exposed significant weaknesses in existing legal structure, treatment procedure, police, laboratory, and community support facilities. It is a case in which illicit science, serviced by abundant and relatively inexpensive technical supplies, has moved beyond the thought and preparation of the legitimate community. There is a need for a more rapid, tightly organized response.

There is yet another dimension to the problem of clandestine manufacture that must be realized. It is increasingly an international problem in which all of the weaknesses exposed in the United States at the national level, are greatly magnified. Clandestine manufacture of methamphetamine has existed for some years in both Europe and Asia and appears to be significantly increasing. In 1987, the number of such laboratories seized nearly doubled in the Federal Republic of Germany. A large methamphetamine laboratory was seized for the first time in Thailand. 3,4-Methylendioxymethamphetamine (MDMA), one of the "designer drugs" of the United States, has been seized in Canada, Mexico, Australia, and Central and South Americas and a number of European countries. A laboratory responsible for the manufacture of more than six million dosage units was seized in Mexico in 1987. It appears that the precursor chemicals came from Europe. A suspect citizen of an European country recently purchased all of the chemicals and laboratory equipment necessary for the manufacture of methaqualone and shipped them all to an unsuspecting and previously unequipped African country.

The skill, precursors and equipment for the manufacture of a great variety of dangerous drugs of abuse are all cheaply and legally available in international commerce and can be quickly moved to any desired location. There are many areas of the world in which such operations can be pursued without fear of interference by authorities. In many cases, manufacture and distribution of the drugs would not violate the law. In most countries, the drugs could not be detected or identified in existing facilities. In virtually every society, there is sufficient money to provide a profitable market for such drugs in view of the extremely small dosage unit cost of manufacture. Finally and regrettably, an increasingly significant number of people in all societies are susceptible to the abuse of drugs which are made available to them. Many of these developments are as yet represented by isolated cases. What can happen has not yet happened. Responsible officials must realize what they face and what is to be done.

It is with the intention of initiating this process that the Drug Enforcement Administration has joined with the World Health Organization in sponsoring this first International Conference of Experts on the Problems of Controlled Substance Analogues.

Designer Drugs: The California Experience

Gary L. Henderson, Ph.D.

In the last week of December, 1979, two very unusual apparent overdose deaths occurred in Orange County, California. Both victims had histories of heroin use, were found with paraphernalia, and autopsy findings of pulmonary edema and "tracks" were consistent with heroin overdose. Surprisingly, toxicological analysis of the body fluids showed that no drugs were present. Over the next few months six additional similar overdose deaths occurred in Orange County and by the end of 1980 there was a total of 10 deaths, all of which appeared to be classic narcotism deaths, yet no drug could be found. During this same period, law enforcement officials seized a number of street samples being sold as heroin, but which contained no heroin or, in fact, any other drug. A common link between these events was a drug called "China White" which the overdose victims were buying and the dealers were selling.

Initially, the material sold as "China White" was reported as containing the compound 3-methylfentanyl (Kram *et al.,* 1981). This initial identification proved to be incorrect and the drug was later correctly identified as alpha-methylfentanyl (Figure 1). Alpha-methylfentanyl is an analogue of fentanyl, a very potent narcotic analgesic synthesized in the early 1960's by the Janssen Pharmaceutica Research Laboratories in Belgium and used throughout the world as an intravenous anesthetic/analgesic (Janssen, 1963; Gardocki *et al.,* 1964; Janssen, 1965; Reneman, 1979).

Illicit synthesis of drugs of abuse is not new. Since the 1960's, clandestine laboratories have been producing drugs such as lysergide (LSD), phencyclidine (PCP), amphetamine and methamphetamine. Now, for the first time illicit laboratories were producing original narcotic drugs, not illicit copies of pharmaceutical products. Even though alpha-methylfentanyl is chemically and pharmacologically nearly identical to fentanyl (alpha-methyl-fentanyl has the same pharmacological properties, but is twice as potent as fentanyl as an analgesic), it was technically a new chemical entity, not listed in any schedule of the U.S. Controlled Substances Act, and therefore not a controlled substance. In fact, alpha-methylfentanyl remained uncontrolled until 1981 when it was classified as a Schedule I drug (46 FR 46799, 1981).

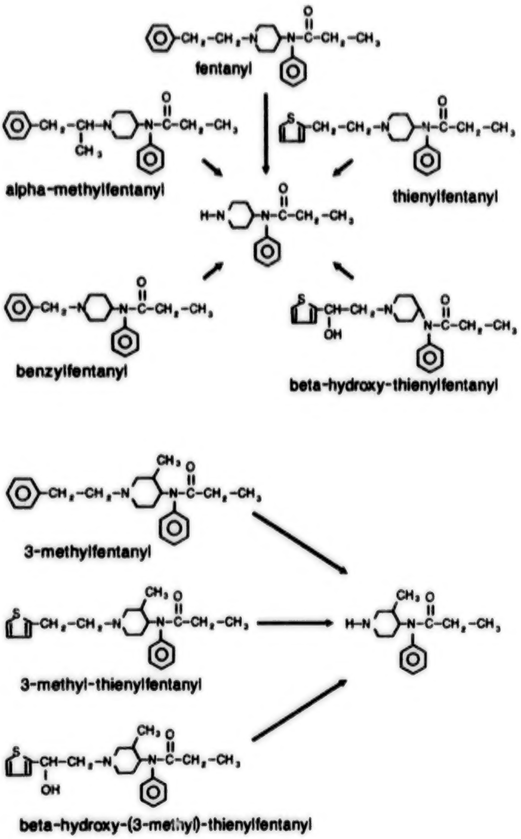
The laboratory of the University of California-Davis, School of Medicine, Department of Pharmacology, which had developed a very sensitive and very specific radioimmunoassay (RIA) for fentanyl (Henderson *et al.*, 1975) was therefore asked to investigate these unexplained overdose deaths. This assay was first used in pharmacokinetic studies in surgical patients shortly after fentanyl was introduced into clinical medicine (Schleimer *et al.*, 1978). In 1976, it was learned that fentanyl was being used to "dope" race horses (Stumes, 1978). Therefore, the procedure was then modified to detect the drug in race horses (Henderson *et al.*, 1981). In addition the primary metabolite of fentanyl in the horse was isolated and identified (Frincke and Henderson, 1983).

When body fluids of overdosed "China White" victims were examined by RIA, a fentanyl-like compound was identified and it was confirmed to be alpha-methylfentanyl. The drug was present in blood and urine in very small concentrations, between 1 and 10 nanogram equivalents of fentanyl per milliliter. Powder samples generally contained about one microgram per gram (Henderson, 1983). By the time alpha-methylfentanyl was placed into Schedule I (September 22, 1981), another analogue of fentanyl appeared—para-fluorofentanyl. This compound has approximately the same analgesic potency as fentanyl and appeared on the street only briefly. In the spring of 1984 another analogue was identified—alpha-methylacetylfentanyl. Although this new analogue was very similar to alpha-methylfentanyl, it too was technically a new chemical entity, and therefore not a controlled substance. Street samples of this compound were always found to be contaminated with the acryl analogue which is probably a by-product formed during synthesis. Alpha-methylacetyfentanyl is less potent than fentanyl (about ten times as potent as morphine), but longer-acting than fentanyl (just slightly shorter-acting than morphine).

The succession of new fentanyl analogues appearing on the streets continued. In 1983, 3-methylfentanyl was identified in powder samples found near a suspected drug overdose victim. The appearance of this fentanyl analogue on the street was yet another surprise for although the structure of 3-methylfentanyl was similar to previous analogues (Figure 1), it was extraordinarily more potent. 3-Methylfentanyl may be the most potent analogue of the fentanyl series and one of the most potent narcotic analgesics known. According to Janssen Pharmaceutica, who had reported on its synthesis and pharmacological properties in rodents, the (+)-cis isomer of 3-methylfentanyl is approximately 7,000 times as potent as morphine while the (±) trans isomer is approximately 1,000 times as potent (Van Bever *et al.*, 1974).

At this point, the number of fentanyl overdose cases sent to the laboratory increased dramatically. During 1983, approximately one fentanyl case every two months was identified; during 1984 this number quickly rose to one case each week (Figure 2). Concentrations of new analogue(s) in body fluids were at or below the one nanogram per milliliter level, much lower than for the previous analogues. Also all samples, body fluids, powder samples and paraphernalia contained both the *cis* and *trans* isomers of 3-methylfentanyl and fentanyl. Fentanyl is most likely present as a by-product of the synthesis, resulting from the incomplete methylation of the piperidine ring at the 3-position. 3-Methylfentanyl disappeared almost as quickly as it appeared. It was readily available in California from 1983 until the spring of 1985, then virtually disap-

Figure 1

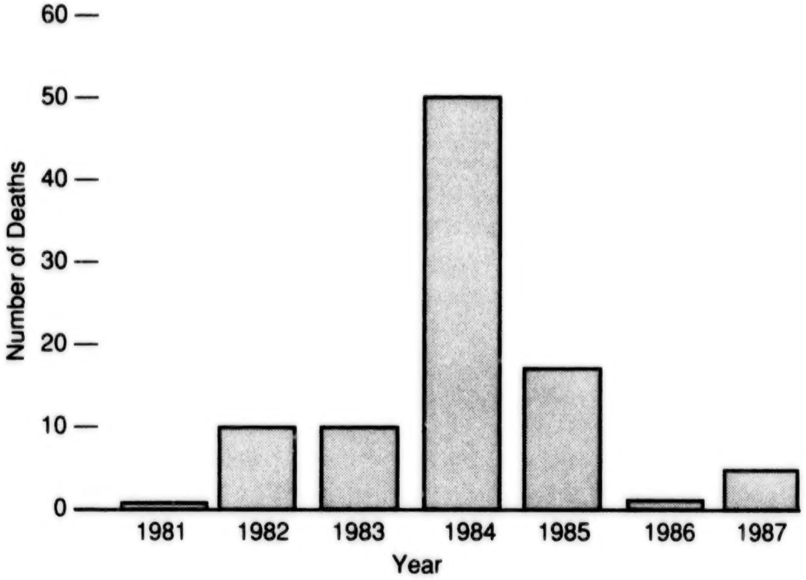


Chemical structures of the illicit fentanyls and their normetabolites.

peared from the streets. Both the incidence of fentanyl analogue overdose deaths and the number of street samples containing fentanyl analogues decreased sharply. Even more surprising, the 3-methyl analogue was replaced by a mixture of heretofore unknown fentanyl analogues. The last powder samples of "China White" obtained in 1985 did not contain 3-methylfentanyl, but contained a complex mixture of beta-hydroxy-, alpha-methyl-, and 3-methyl-substituted fentanyls and thienylfentanyls (Figure 1).

Fentanyl itself is sold on the street and used as a heroin substitute. This material appears to be of clandestine origin, rather than diverted pharmaceutical stocks because it is usually found mixed with nearly equal amounts of benzylfentanyl. Benzylfentanyl is not pharmacologically active as a narcotic, but it is a logical precursor for the synthesis of

Figure 2



Number of fentanyl-related deaths identified each year by the U.C.D. laboratory.

fentanyl. At the present time, the fentanyl/benzylfentanyl mixture is the only illicit fentanyl available and is confined primarily to the San Diego area. During the first six months of 1987 four fentanyl-related deaths, including three overdose cases in California and one in Nevada, have been identified. In two of the cases, a fentanyl/benzylfentanyl mixture was identified in the body fluids and accompanying paraphernalia. In the other two cases the victims were health professionals and their deaths appeared to be the result of abusing pharmaceutical fentanyl.

Methods of Analysis

All samples were examined initially with the RIA screening method and, when sufficient sample was available, positive samples were confirmed by gas chromatography (GC) with electron capture detection (ECD) or mass spectroscopy (MS). Samples (1 ml blood or urine, 10 mg powder) were first made basic with 1 ml of one normal sodium hydroxide, then extracted with 4 ml of n-heptane. Solvent was evaporated under nitrogen and the residue reconstituted in methanol for RIA, GC-ECD, or GC-MS analysis.

RIA

Most of the samples were screened by the liquid phase ^{3}HRIA system described previously (Henderson *et al.*, 1975; Schleimer *et al.*, 1978). Recently a solid phase RIA using ^{125}I-labeled fentanyl and antisera immobilized on polypropylene tubes had been used (Diagnostic Products Corporation, Los Angeles, CA).

Gas Chromatography

Gas chromatographic separation of the various fentanyl analogues and derivatized normetabolites was best achieved using a fused silica capillary column (DB–1701, 15 m X 0.25 mm I.D.), helium as the carrier gas (1 ml/min) and column temperatures in the range of 190–200° C.

Mass Spectroscopy

Mass spectroscopy was used for confirmation of the various fentanyl analogues and the derivatized normetabolites. Analyses were carried out using a ZAB–HS–2F double focusing mass spectrometer (VG Analytical, Wythenshawe, UK) directly interfaced with a Hewlett-Packard 5790A gas chromatograph.

Electron Capture Detection

Normetabolites of fentanyl and 3-methylfentanyl were detected by gas chromatography-electron capture detection using a recently developed derivatization technique (Hammargren and Henderson, 1987). Urine samples (1 ml) were partially purified by differential pH extraction, then reacted with pentafluoropropionic anhydride (PFPA) in a two phase system (methylene chloride and urine saturated with sodium bicarbonate). The resulting pentafluoropropionamides were chromatographed on a DB–1701 capillary column and detected with a ^{63}Ni electron capture detector. Calibration curves were generated by analyzing urine samples fortified with the normetabolites (2–32 ng/ml) and dieldrin (50 pg/μl) as the internal standard. Limit of detection for this method is 2 ng/ml for norfentanyl and nor-3-methylfentanyl.

Results

Since 1980, nearly 4,000 blood and urine samples have been analyzed for the presence of fentanyl and its analogues in the University's laboratory. Samples were obtained from three sources: coroner's and toxicology laboratories, methadone maintenance and other drug treatment programs, and state and county law enforcement officials. In each case heroin use was suspected, but no drug could be detected by routine toxicological analysis. It is important to remember that the samples analyzed and reported herein were not obtained as part of a systematic study, but rather are only a collection of samples referred to the laboratory. Nevertheless, because a large number of samples were obtained from nearly every part of California over a seven year period, the data does describe, in general terms, a picture of fentanyl abuse in the State of California.

Powder Samples

The physical appearance of powder samples sold as "China White" is as diverse as the names under which they are sold. Samples contained very small amounts of the various fentanyl analogues diluted (cut) with large amounts of lactose or mannitol. Amount of active drug present was exceedingly small, generally less than one percent, and therefore contributed nothing to the color, odor, or taste of the sample. Color ranged from pure white (sold as "Persian White") to an off-white or light tan (sold as "China White", "Synthetic Heroin", or "Fentanyl"), to light or dark brown (sold as "Mexican Brown"). The brown color apparently comes from lactose which has been heated and slightly caramelized. Texture of the samples ranged from light and finely powdered to somewhat coarse, cake-like and crumbly, somewhat resembling powdered milk. Occasionally, samples had a medicinal or chemical odor, but this is not characteristic. In summary, the fentanyl analogues have appeared in all the various forms that heroin does and there is nothing about the appearance of any sample that will identify it as containing fentanyl.

Most of the powder samples analyzed contained more than one compound. Samples which contained 3-methylfentanyl always contained fentanyl, typically in a ratio of 1.4: 1: 0.25 for fentanyl, *cis*-3-methylfentanyl, and *trans*-3-methylfentanyl, respectively. Samples that contained fentanyl also contained benzylfentanyl in approximately equal amounts. Some samples contained cocaine; these were generally cut with mannitol. Fentanyl analogue users have reported that the drug was available in two forms: one form for "shooters" (intravenous administration) and another for "snorters" (intranasal administration).

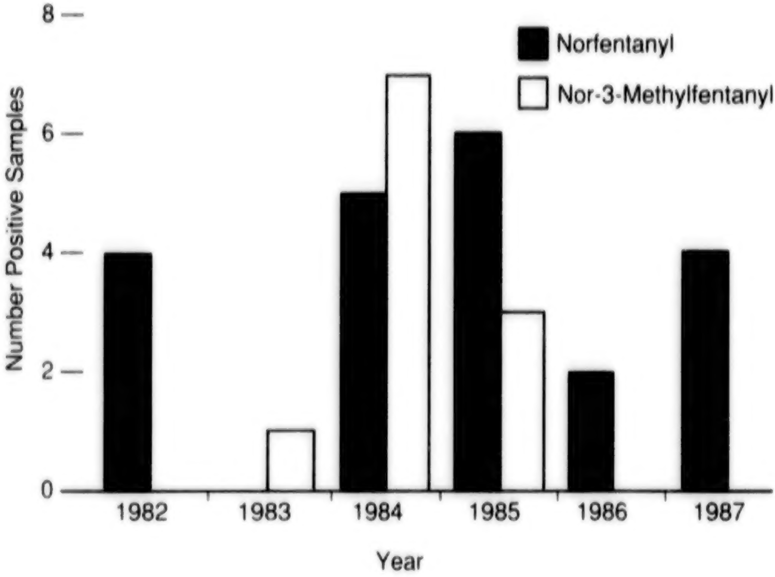
Overdose Cases

To date, 110 fentanyl-related overdose deaths have been identified in the laboratory. All deaths occurred in California with the exception of two cases in Portland, Oregon (1983), one case in Tempe, Arizona (1980), and one case in Reno, Nevada (1987). The first death occurred in December, 1979 and the most recent death occurred in February, 1987.

Figure 3 shows the number of samples found each year containing either norfentanyl (from alpha-methylfentanyl or fentanyl use) or nor-3-methylfentanyl. Figure 4 compares the concentrations of the parent drugs (determined by RIA) to those of the normetabolites (determined by GC-ECD).

Figure 3

Urine Samples from Overdose Cases

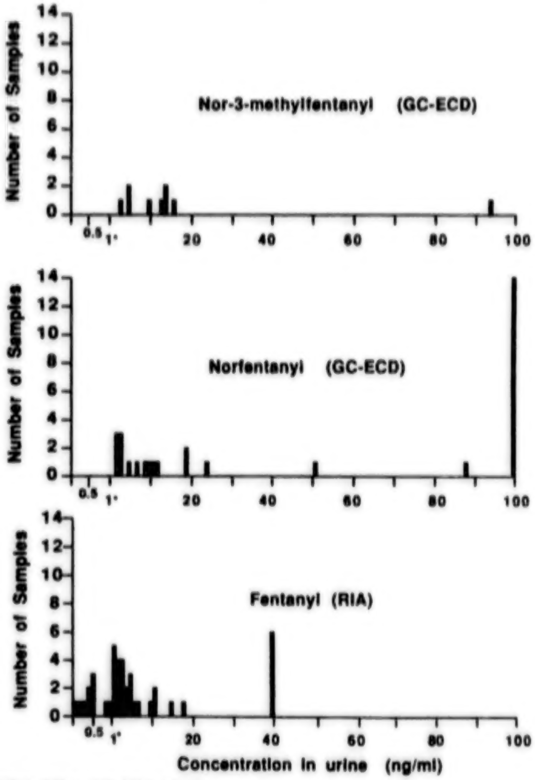


Distribution of urine samples containing either norfentanyl alone or nor-3-methylfentanyl. Samples were submitted by coroner's and toxicology laboratories and were associated with suspected drug overdose deaths. Solid bars indicate the number of urine samples each year which contained only norfentanyl. Open bars indicate the number of urine samples which contained nor-3-methylfentanyl.

Norfentanyl was found every year from 1982 to the present while the nor-3-methylfentanyl metabolite was found only from 1983 to 1985. Every sample that contained the "normetabolite" of 3-methylfentanyl, also contained norfentanyl. Further, the average norfentanyl: *cis*-nor-3-methylfentanyl ratio in these samples was 1.4, which is exactly the fentanyl: 3-methylfentanyl ratio found in powder samples. Urine concentrations of norfentanyl ranged from 2 to nearly 4,000 ng/ml and nor-3-methylfentanyl concentrations ranged from 2 to 94 ng/ml.

It is surprising that during the period 1983–1985, when the 3-methyl analogue was widely available, nor-3-methylfentanyl (and norfentanyl) in 11 cases and norfentanyl alone were found in an equal number of cases. Over the eight-year period of collection and analyses of samples, norfen-

Figure 4



*Note shift in scale below 1 ng/ml.

Concentrations of fentanyl, norfentanyl, and nor-3-methylfentanyl in urine samples from overdose victims. Fentanyl concentrations were determined by RIA. Note there is a shift in scale below 1 ng/ml and that values shown at 40 ng/ml actually represent samples at or above this value which is the upper limit on the calibration curve. Norfentanyl and nor-3-methylfentanyl concentrations were determined by gas-chromatography-electron capture detection. Values shown at 100 ng/ml for norfentanyl actually represent samples at or above this value.

tanyl was found in nearly three times as many overdose cases as was nor-3-methylfentanyl. This distribution is unexpected considering the fact that the 3-methyl analogue is approximately 20 times as potent (ED_{50} 0.00058 mg/kg compared with 0.011 mg/kg for fentanyl, rats, iv tail withdrawal test) and 8 times longer-acting (four hours compared with 0.5 hours (Van Bever *et al.,* 1974)). However, these data do support the findings by Janssen that, in laboratory animals, the 3-methyl analogue has a much higher therapeutic index than fentanyl. The therapeutic index (LD_{50}/ED_{50}, rats, iv) reported for (+)-cis-3-methylfentanyl, is 1,662 compared with 255 for fentanyl and 75 for morphine (Van Bever *et al.,* 1974)

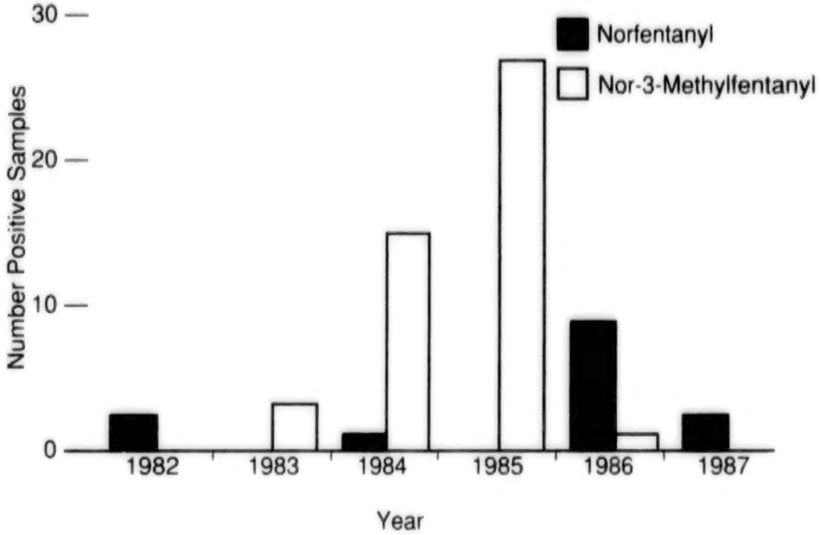
3-Methylfentanyl is a very attractive synthetic heroin substitute indeed. It is relatively easy to synthesize, approximately 1,000 times as potent as heroin with about the same duration of action. It has a rapid onset of action following intravenous or intranasal administration, and in addition has a seven-fold greater therapeutic index.

Samples From Drug Treatment Programs

To date there is data on 60 urine samples from suspected fentanyl analogue users in drug treatment programs. These samples were found positive by the RIA screening test and confirmed by the GC–ECD method. Either norfentanyl or nor-3-methylfentanyl have been identified in all samples and the results are summarized in Figures 5 and 6. Norfentanyl was identified in samples from 1982 to the present, while nor-3-methylfentanyl was found only from 1983 to 1986 (Figure 5). In contrast to the data on the overdose cases, nor-3-methylfentanyl was found almost exclusively during the period 1983–1985. As can be seen from Figure 6, 50 percent of the samples had concentrations below 1 ng/ml as determined by RIA.

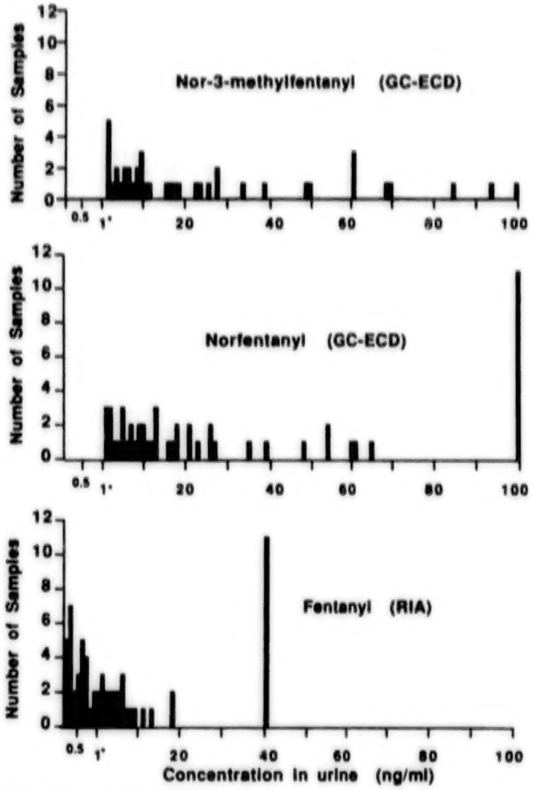
Figure 5

Urine Samples from Drug Treatment Programs



Distribution of urine samples from drug treatment programs containing either norfentanyl alone or nor-3-methylfentanyl. Samples were obtained from individuals suspected of using one of the illicit fentanyls. Solid bars indicate the number of urine samples which contained only norfentanyl. Open bars indicate the number of urine samples which contained nor-3-methylfentanyl.

Figure 6



* Note shift in scale below 1 ng/ml.

Concentrations of fentanyl, norfentanyl, and nor-3-methylfentanyl in urine samples from individuals suspected of abusing one of the fentanyls. Fentanyl concentrations were determined by RIA. Note there is a shift in scale below 1 ng/ml and that values shown at 40 ng/ml, actually represent samples at or above this value which is the upper limit on the calibration curve. Norfentanyl and nor-3-methylfentanyl concentrations were determined by gas-chromatography electron capture detection. Values shown at 100 ng/ml for norfentanyl actually represent samples at or above this value.

Conclusions

The data presented show that the illicit fentanyls have been present in California from 1979 until the present time. Use of these drugs peaked during 1985 and declined rapidly thereafter. The 3-methyl analogue was introduced onto the streets sometime during 1983 and data suggests that it was the principal form of fentanyl available until 1986. Since 1986, the only form of illicit fentanyl available has been the fentanyl/benzylfentanyl mixture found almost exclusively in the San Diego area.

To date, 110 overdose deaths attributed to the fentanyls have been identified. All deaths occurred in California with the exception of two cases in Portland, Oregon (1983), one case in Tempe, Arizona (1980), and one case in Reno, Nevada (1987). The earliest death occurred in 1979 and the most recent death occurred in February, 1987. Investigative reports and coroners' findings from a number of fentanyl overdose deaths have been collected and reviewed in an attempt to determine a profile of the typical fentanyl overdose victim. The "typical" fentanyl overdose victim was young (mean age 30, range 18–49), male (74 percent, 26 percent female), generally employed as a blue-collar worker, and usually found in the bathroom or bedroom of his (her) home by family or friends. Most often he (she) had a prior history of heroin use, but often the family and friends claimed that the individual had not been abusing drugs recently. Generally, no other drugs were found; however, if another drug were present, it was invariably ethanol, most often present at the 0.1 percent level.

This profile suggests that the fentanyls are not distributed within any localized geographical area or to any particular ethnic or age group, but seem to be distributed rather uniformly throughout the addict population. However, the geographic distribution of the fentanyl deaths is somewhat curious. Most deaths occurred in suburban, even rural areas, but not large cities. In fact, there has never been an illicit fentanyl death reported in the city of Los Angeles (the largest city in the state) and there have been only two reported deaths in San Francisco (the second largest city). This unusual distribution remains unexplained but is not the result of underreporting because our laboratory routinely examines body fluids from unexplained overdose cases submitted by the coroners of these two cities.

The relatively few numbers of 3-methylfentanyl-related deaths compared with fentanyl and alpha-methylfentanyl is noteworthy. Data from drug treatment programs suggest that the 3-methyl analogue was the most available form of fentanyl from 1983–1985, yet this analogue is implicated in only one-half of the overdose deaths during this period. Perhaps this reflects the much greater therapeutic index of the 3-methyl analogue.

Future Trends

In view of this author, an increasing number of drugs of abuse in the future will be synthetic rather than plant products. They will be synthesized from readily available chemicals, will be derivatives of pharmaceuticals, will be very potent and often very selective in their action. In addition, they will be marketed very cleverly. "Designer Drugs" may become an international problem. A single gram of any very potent drug like 3-methylfentanyl could be synthesized at one location anywhere in the world, distributed uncut to distribution sites worldwide, and then formulated (cut) into many thousand, perhaps up to a million, doses. Preventing the distribution of such small amounts of material would be exceedingly difficult.

Fortunately, wide distribution of the fentanyls has not yet occurred. Use of the fentanyls has been restricted almost exclusively to California and at the present time they do not appear to be widely available, even in California. However, there were events in 1986 which suggest that the fentanyls could appear at any time and would not be restricted to California. During 1986, at least two, and possibly four, well trained organic synthetic chemists were arrested for synthesizing 3-methylfentanyl (Hays, 1986; Lewis, 1986). Even more disturbing is the fact that they were working in legitimate chemistry laboratories in the eastern United States, not in California. Fortunately, these chemists were apprehended before they were able to distribute any drug. Again it is important to remember that any chemist who achieves even a nominal yield of a few hundred milligrams of the potent fentanyls has at his disposal many millions of individual doses of a synthetic heroin.

Answers to this problem are not readily apparent. The literature abounds with synthetic routes and pharmacological properties of thousands of narcotics, stimulants, hallucinogens, and sedative-hypnotics. This information is readily accessible throughout the world and creative chemists will continue to exploit the pharmaceutical chemistry literature. Restricting access to the literature is not feasible and controlling access to the chemicals needed to make these drugs will be minimally effective. In the past, restricting chemicals has only stimulated clandestine chemists to assemble the drugs from more elementary precursors. Locating these laboratories will be a similarly difficult task. When very potent chemicals are produced, a clandestine laboratory need operate for only a few days to make a few hundred grams of material. Today, the problem is compounded by a new trend in which legitimate chemists are synthesizing illicit drugs in commercial chemical laboratories.

Traditional responses to drug abuse problems seem to offer little promise. In fact, success in curtailing the distribution of natural products such as opium, coca and marijuana and preventing the diversion of pharmaceuticals is likely to be the stimulus for the development of potent synthetic substitutes. The challenge for toxicologists and forensic chemists is to keep pace technologically. Potent drugs of unusual chemical structure will require both broader screening techniques capable of detecting drugs and their metabolites present at the nanogram and picogram levels. Simple answers to this problem are not readily apparent, but they are not likelv to be found unless the problem is first recognized.

References

Federal Register, Vol. 46, No. 183, Tuesday, September 22, 1981.

Frincke, J.M. and Henderson, G.L., The major metabolite of fentanyl in the horse, *Drug Metab. Dispos.* 8: 425-427, 1981.

Gardocki, J.F. and Yelonsky, J., A study of some of the pharmacologic actions of fentanyl citrate, *Tox. Appl. Pharm.,* 6: 48-62, 1964.

Hammargren, W.M. and Henderson, G.L., Analysis of the normetabolites of the fentanyls by gas-liquid chromatography-electron capture detection, submitted by *J. Anal. Tox.,* 1987.

Hays, L., Chemist Charged in Drug Scheme, Washington Post, Jan., p. A4, 1986.

Henderson. G.L., Frincke, J., Leung, C.Y., Torten, M. and Benjamini, E., Antibodies to fentanyl, *J. Pharm. Exp. Therap.* 192: 489-496, 1975.

Henderson, G.L., Frincke, J.M., Garber, R.J., and Knight, H.M., Metabolism of fentanyl in man and the horse, *Proc. West. Pharm. Soc.,* 24: 137-140, 1981.

Henderson, G.L., Blood concentrations of fentanyl and its analogs in overdose victims, *Proc. West. Pharm. Soc.,* 26: 287-290, 1983.

Janssen, P.A.J., Niemegeers, C.J.E., Dony, J.G.H., The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats, *Arzneim. Forsch.,* 13: 502-507, 1963.

Janssen, P.A.J.: U.S. Patent 3,164,600, 1965.

Kram, T.C., Cooper, D.A., and Allen, A.C., Behind the identification in China white, *Anal. Chem.,* 53: 1379-1386, 1981.

Lewis, N., Chemist Sentenced in D.C. Drug Case, *Washington Post,* November 29, p. C1., 1986.

Reneman, R.S., van der Vusse, G.L., Xhornneux, R. and van Gerven, W., The use of high doses of analgesics during anesthesia—a general review, In: *Analgesia in Anesthesia and Obstetrics,* Proceeding Boerhaave Course, Leiden, Belgium, 35-52, 1979.

Schleimer, R., Benjamini, E., Eisele, J., and Henderson, G.L., Pharmacokinetics of fentanyl as determined by radioimmunoassay, *Clin. Pharm.,* 23: 188-194, 1978.

Stumes, L., Race tracks tackle a drug problem, *San Francisco Chronicle,* December 26, p. 50, C1, 1978.

Van Bever, W.F.M., Niemegeers, C.J.E., and Janssen, P.A.J., Synthetic analgesics, synthesis and pharmacology of the diastereoisomers of N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide and N-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide, *J. Med. Chem.,* 17: 1047-1051, 1974.

Acknowledgments

This work was supported in part by a contract from the California Department of Alcohol and Drug Programs, Number D-0049-3.

Statistics and Trafficking Patterns of Drugs and Chemicals

Terrance W. Woodworth and Ian Bain

Introduction

The International Criminal Police Organization (OIPC-INTERPOL) is an intergovernmental organization, primarily directed toward the prevention of crime and enforcement of the laws governing criminal activity. This includes crimes against persons and/or property, drug-related crimes, and economic and financial crimes. Examples are terrorism, drug trafficking, stolen art objects, bank fraud, customs violations, mail fraud, and the counterfeiting of currency.

Currently, there are 142 member countries of the INTERPOL organization. When a country becomes a member, it establishes a national "INTERPOL" office within the member's law enforcement structure. These offices are referred to as NCB's or National Central Bureaus. For example, the NCB for the Federal Republic of Germany is located within the Bundeskriminalamt, the Federal Criminal Police Office for the Federal Republic of Germany.

The permanent administrative and technical institution through which the INTERPOL Organization operates is the General Secretariat located in St. Cloud, France. Within the General Secretariat, under the Police Division, is the Drugs Sub-Division. The Drugs Sub-Division performs a variety of functions, all of which are intended to assist the national drug services in each of the member countries in combatting international drug trafficking. The Drugs Sub-Division is the largest single unit of police officers with representatives from about twenty different countries. The General Secretariat itself has offices from approximately forty different countries.

In addition to the responsibilities associated with fighting heroin, cocaine, and cannabis trafficking, the Drugs Sub-Division is responsible for activities associated with other narcotic drugs and psychotropic substances. These responsibilities pertain to the regulation, control, and intelligence collection in five primary drug categories:

1. The legitimately manufactured narcotic drugs, such as codeine, morphine, and pethidine (meperidine), which are subject to the provisions of the Single Convention on Narcotic Drugs, 1961;

2. The legitimately produced psychotropic substances, such as amphetamines, barbiturates, and benzodiazepines, which are regulated by the Convention on Psychotropic Substances, 1971;

3. The illicitly produced psychotropic substances, such as ampheta-

mine, methamphetamine, and lysergide (LSD), which are also controlled under the Psychotropic Convention;

4. The legally and illegally produced precursors and essential chemicals, such as phenyl-2-propanone (P2P), acetic anhydride, and ethyl ether, which are used to manufacture certain narcotics and psychotropic substances; and

5. The illicitly produced controlled substance analogues, such as the narcotics MPPP and alpha-methylfentanyl, of which only a few are controlled internationally.

Data and Information Collection

A major portion of the Drugs Sub-Division's activities is devoted to cooperating and interacting with other international organizations such as the Customs Cooperation Council, the United States Division of Narcotic Drugs, the International Narcotics Control Board, and the World Health Organization. For example, the OIPC-INTERPOL Organization has for many years worked very closely with the World Health Organization in its substance reviews for international control purposes. Several times a year, the World Health Organization requests that OIPC-INTERPOL query its 142 members concerning the abuse and illicit trafficking of select substances which are being reviewed. Data and information are collected from OIPC-INTERPOL members by the General Secretariat and a formal report is then prepared and submitted to the World Health Organization. This example of data collection identifies one of the Drugs Sub-Division's information sources relating to illicit drug trafficking which are as follows:

1. On a daily basis, the General Secretariat receives messages from its member countries concerning on-going drug investigations conducted by a member country or jointly by several members. This information is reviewed by a Drug Liaison Officer and an Intelligence Officer for appropriate action by the Drugs Sub-Division. A synthesis of the investigation is prepared and entered in the General Secretariat's computer system;

2. On a daily basis, the General Secretariat receives messages from its member countries concerning seizures of drugs or substances and arrests of traffickers. This information is also passed to a Drug Liaison Officer, an Intelligence Officer, and entered in the General Secretariat's automated system;

3. Within the Drugs Sub-Division, Drug Liaison Officers are assigned specific responsibility for geographic regions of the world. These officers are continually in contact with the NCB's in their area of responsibility and are frequently sent on missions to member countries where information on trafficking trends and developments is collected.

4. On a regular basis, the Drugs Sub-Division conducts special studies of certain drugs, such as those required for the above mentioned

World Health Organization substance reviews as well as, various training programs and working group meetings. A working group meeting, for example, would include a situation where, because of the volume of information available at our records center, the Drugs Sub-Division is asked to conduct an in-depth analysis of particular traffickers or groups of traffickers. The Drugs Sub-Division would then host a working meeting of the concerned NCB officers at the General Secretariat for the purpose of exchanging information and developing a common strategy to attack and immobilize the trafficking organization; and

5. Each year the member countries submit a lengthy Annual National Statistical Report detailing such facts as the numbers and nationalities of persons arrested, the number of clandestine laboratories neutralized, and the number of drug seizures and the quantities seized.

Current Developments in Illicit Drug Trafficking

The information provided from the above five sources paint a dismal picture of recent developments in drug trafficking. Not only has there been an increase in volume, but a geographic expansion has also occurred. Additionally, the drug trafficker is an ingenious character and increasingly complex and sophisticated methods of drug diversion are being seen. Consequently, if government's method of control, regulation, and investigation do not change, the situation can only get worse.

The General Secretariat cannot relate every aspect of the drug trafficking situation, nor identify every new trend or method. That information is simply not available. Although OIPC-INTERPOL's information is very good and quite valuable, it is recognized as being fragmented. It is unrealistic to expect, for example, that all 142 INTERPOL members be equally efficient in providing information to the General Secretariat as well as equally efficient in cooperating with other countries. Yet, in spite of its imperfections, the OIPC-INTERPOL data base on drugs and criminality on the international level is unique in this field.

The legitimately manufactured pharmaceutical narcotics, controlled under the Single Convention, have decreased in appearance in international traffic in both of the last two years. Some countries, especially the United States, continue, however, to experience domestic diversion and abuse of drugs such as codeine, oxycodone, and hydromorphone. Yet seizures in international traffic reported to INTERPOL of the legally-made narcotic drugs declined from several million dosage units in 1984 to approximately 300,000 dosage units in 1985; and declined again in 1986 to just over 200,000 dosage units. In 1987, other than several small seizures of methadone—frequently emanating from the Netherlands—international seizure reports concerning the pharmaceutical narcotics have not been received.

The legally-made, psychotropic substances appeared in the illicit traffic in virtually every area between 1986 and September 1987. The seizures most frequently reported to the General Secretariat were the various amphetamine types; the allegedly discontinued, Bulgarian aspirin-ampetamine; fenethylline; amfepramone (diethylpropion); secobarbital; methaqualone; and several of the benzodiazepines. The most widespread abuse and trafficking was reported for the benzodiazepines. Significant seizures in international traffic were effected in Greece where almost 70,000 dosage units of flunitrazepam were recovered in two cases in 1986. In October 1986, 40,000 dosage units of flunitrazepam were seized in one case in Switzerland. France and Spain have reported numerous small seizures of flunitrazepam in the first seven months of 1987. Additionally from the 1986 Annual National Statistical Reports, over fifteen million dosage units of benzodiazepines were seized and reported from every continent. In 1986, Greece alone reported seizures of over 59 kilograms of diazepam. In 1987, Israel notified the General Secretariat of the abuse of benzodiazepines in their country and the unprecedented mixing of flunitrazepam with methadone by drug abusers. Singapore, Indonesia, the Philippines, Thailand, and Malaysia have reported significant abuse of the benzodiazepines. Malaysia has banned flunitrazepam, and nitrazepam reportedly is filling the void created by this action. The Philippines has also noted the increased abuse of dextromethorphan mixed with ephedrine.

The Federal Republic of Germany reported a 3.7 kilograms seizure of amfepramone in March 1987 and a month afterwards, a shipment of 85 kilograms of amfepramone enroute to Spain was stolen at the Frankfurt airport.

Fenethylline, recently controlled in Schedule II of the Psychotropic Convention, continued to pose a tremendous problem for authorities in the Near and Middle East with seizures of approximately twenty million dosage units in 1986. The seizures of fenethylline in this area of the world continue in 1987 and in June of 1987 Turkey reported a seizure of 1,043,000 dosage units of fenethylline destined for the Middle East. Secobarbital was also frequently seized in the Near and Middle East with reports of over two million dosage units confiscated in 1986.

Almost eleven million (11,000,000) dosage units of methaqualone were seized worldwide in 1986. This is significant in light of diminished production by many countries and the outlawing of this substance by many others. Reports of large seizures of methaqualone (dosage units) in 1986 were received from India (6.7 million), the Federal Republic of Germany (just under one million), Hong Kong (408,705), the United States (706,531), and African countries (450,000). It is interesting to note that negotiations between Hong Kong and China resulted in the banning of the legitimate manufacture of methaqualone by the Chinese Ministry of Public Hygiene in May 1987.

Perhaps the most frightening trend in the last two years has been the enormous flow of psychotropic substances into the developing African nations. Seizures of methaqualone, amphetamines, and secobarbital were 10 times the seizures of heroin and cocaine combined, for that continent, for both 1985 and 1986. Additionally, large seizures of ephedrine, 91,200 by Mali in April 1987, and other stimulants have been seen throughout the African continent. Investigative reports reveal that millions of dosage units of the internationally uncontrolled substance, pemoline, are entering Nigeria from Yugoslavia and the Netherlands, shipped through the United Kingdom.

The third category, the illicitly produced psychotropic substances, continues to be primarily a problem facing the industrialized regions of the world. However, this trend is changing too with the reported seizure of a portable, methaqualone laboratory in the back of a trailer truck in South Africa in February 1987. The largest quantities and most frequently reported seizures of clandestinely manufactured psychotropics are, by far, amphetamine and methamphetamine. Europe, North America, and Eastern Asia appear to be the most affected, although illicitly produced amphetamine has surfaced with increasing frequency in South America, the Pacific, Africa, and the Middle East. Little evidence exists, however, that these substances are extensively trafficked beyond the geographic region in which they are manufactured. Yet there is always an exception to every general trend and such was the case in the summer of 1987 when Japan seized 53 kilograms of amphetamine which was shipped to Japan from Hawaii. Japan, it should be noted, seized over 250 kilograms of amphetamines in 1986; and Thailand seized 14.5 kilograms in 1986. Both countries experienced this continued increase of amphetamine trafficking through September 1987. In Europe, 350 kilograms of amphetamine were seized in 1986: 55 Kilograms in the United Kingdom, 110 kilograms in the Scandinavian countries, 84.5 kilograms in the Federal Republic of Germany and 86 kilograms in the Netherlands. This is a huge increase over 1985 amphetamine seizures and the European countries are quite concerned about this trend. Methamphetamine seizures were reported by the Federal Republic of Germany, Austria, Italy, and Japan. However, the most effected region was the United States, reporting seizures of over 31 million dosage units of methamphetamine in 1986. PCP, however, was the most frequently mentioned substance by U.S. hospital emergency rooms and medical examiners in 1986.

Seizures of LSD around the world skyrocketed from 200,000 doses in 1985 to over four million doses seized in 1986. In Europe, LSD seizures were reported by almost every country. The Netherlands has continued to be an important distribution point in Europe, but the seizure of several LSD operations in the Netherlands in 1985 and 1986 accounted for a significant drop in LSD seizures in Holland for 1986. However, LSD activities in Spain are circumspect with seizures of over 67,000 dosage units in 1986. The increased LSD trend continues in the United States too with amost four million (4,000,000) LSD doses seized in 1986. Zimbabwe also reported seizing 105 doses of LSD in 1986.

New Zealand and Australia continued to experience problems with the "back-conversion" of codeine into morphine and then heroin, seizing 63 such laboratories in those two countries in 1986.

The problem with illicitly produced psychotropic substances is underscored with the fact that 657 clandestine laboratories (excluding opiates, cocaine, and hashish oil) were reported seized in 1986. This is a substantial increase over the number of clandestine laboratores seized in 1985. The General Secretariat also continues to receive reports of clandestine methaqualone laboratories. Four (4) such laboratories were dismantled in the United States in 1986 and Hong Kong reports that clandestine operations in that region are producing methaqualone in capsule form. A dozen INTERPOL members reported frequent seizures of heroin which was mixed with methaqualone and other substances during 1986. Diazepam and secobarbital continue to be ingredients found in fake methaqualone tablets.

Trafficking in precursors and essential chemicals continues to escalate and causes unique enforcement problems for police and regulatory authorities. These generally unregulated products flow freely in great volume in the legal as well as the illegal commerce. It is apparent that the Conventions do not provide adequate control over precursors and essential chemicals. As evidenced by the multi-fold increases in the numbers and quantities of seizures of illicitly produced psychotropic substances and the number of clandestine laboratories dismantled—the volume of chemicals diverted for illicit use is obvious. Very simplified, but clear, is the trend over the years that as efforts have affected the availability and purity of heroin, cocaine, and marijuana, a portion of the abusing population turned toward legitimate pharmaceutical substances. Now, with some successes in the control of both the pharmaceutical drugs and the illicit drugs, certain factions of the abusing population have turned toward illicit manufacture. This is not a new trend, but it is a new increase; and generally unregulated access to precursors and essential chemicals is an integral part of this new increase.

INTERPOL continues to receive information about large seizures and trafficking in acetic anhydride, ethyl ether, methylamine, phenyl-2-propanone (P2P), phenylacetic acid, ephedrine and other chemicals. A recent cooperative case involving the Federal Republic of Germany, Belgium, and the United States resulted in the arrest of 28 individuals and the unconfirmed seizure of 28 gallons of P2P. Several individuals arrested were associated with known organized crime elements in the United States and this illegal importation operation of P2P extended over a lengthy period of time. In Europe, in early 1987, Denmark seized 30 liters of P2P and 30 liters of methylamine in one case.

Many countries have initiated programs to counter the movement of precursors and essential chemicals in illicit trade, such as tracking programs and liaison programs with the chemical industry. Other countries have actually placed controls on some of the chemicals and precursors—P2P in the Federal Republic of Germany, the United Kingdom, the United States, the Netherlands, France, Japan, Sweden, and Denmark; piperidine in the United States; and acetic anhydride in Hong Kong and Thailand. A very interesting effort initiated by Sweden involves the cooperation and exchange of information among many of the Northern European and Nordic countries in combatting the illicit amphetamine production in that region. There is a unified effort to share and collect information emanating from each country's tracking chemical liaison programs, coupled with a "signature" type program where seizures over one kilogram of amphetamine are being examined for impurities and other characteristics with the aim of identifying the clandestine operation. This operation has been showing excellent results.

The discouraging information from this and other programs, is that the trafficker is now making his own precursors and essential chemicals—P2P in Europe and acetic anhydride in Thailand. Two laboratory seizures in Thailand, one in late 1986 and one in early 1987, evidenced the production of acetic anhydride utilizing acetaldehyde diacetate.

The final category, the controlled substance analogues or "designer drugs" as they have been called, is a recent and extremely dangerous development. To date, INTERPOL has not received any reports on the illicit narcotic analogues from its members, other than the United States. In 1986 and through August 1987, the General Secretariat was informed of numerous seizures of a nonnarcotic "designer drug" 3,4-methylenedioxymethamphetamine (MDMA) in Spain, Switzerland, Sweden, the Netherlands, Australia, the United Kingdom, the United States, and Canada. Clandestine laboratories making MDMA have been seized in the United States, the Federal Republic of Germany, and the United Kingdom. The abusive spread of this "designer drug" should put us on the alert concerning the narcotic analogues.

Conclusion

Each one of the above five categories involves a different type of drug or substance; and each category presents a unique set of problems relating to enforcement and investigative techniques, specialized knowledge and experience, different sources of information, and a different legal approach. While it is true that the largest diversion of drugs and substances occurs at the international level, it is also true that it is the national authorities who have the jurisdiction, the power, and the ultimate responsibility to address the problem of drug trafficking. However, no one nation or group of nations can tackle this problem alone.

BLANK PAGE

The Activities of the Laboratory of the United Nations Division of Narcotic Drugs in Supporting International Drug Control

Cherif M. Kouidri, Ph.D.

Introduction

From the international standpoint, the question of technical aspects of drug control has been a concern to the United Nations from as early as 1954 when, in accordance with resolution 834 (IX), the General Assembly of the United Nations established the Laboratory of the Division of Narcotic Drugs (DND). Since then, the laboratory's activities have developed according to the recommendations of the Commission on Narcotic Drugs (CND) and have included research on opium, cannabis, khat and optimal codeine production.

Today, the main functions and priorities of DND's Laboratory have been redefined to take due account of the substantial changes in the world drug situation and to respond to the new requirements.

Training of Scientists

The laboratory chemist at the national narcotics or forensic laboratory identifies and analyzes suspected material seized from the illicit drug traffic and prepares evidence for legal proceedings. These activities require accuracy and precision in order to ensure the prosecution of guilty persons and, also, the protection of innocent persons. Therefore, laboratory chemists who are assigned such tasks must possess at least basic skills in methods of identifying and analyzing narcotic and psychotropic substances. If such skills are lacking, those chemists should be given the opportunity to acquire them. The trained chemists would then ensure proper application of analytical techniques to the identification and analysis of materials most commonly encountered in their respective country or region, and provide continuous operation and maintenance of the equipment available to them.

Recognizing the need for the improvement of the professional skills of the staff of international narcotics laboratories in developing countries and responding to the wishes of the Commission on Narcotic Drugs, the DND Laboratory has been providing basic training in methods for the identification and analysis of drugs seized from the illicit traffic since 1958.

Today, in designing and implementing training programs, emphasis is placed on group training, based on common language or geographical region to which the trainees belong. Also, due account is given to the variations in the qualifications of trainees, the frequent lack of uniformity in the equipment available in their respective national laboratories and the scarcity of the necessary technical and scientific information in developing countries. These considerations have made it necessary to establish standard requirements for effective training so that the knowledge gained can be immediately put to use on the return of the trainees to their own countries.

To date, 218 chemists from 79 countries have received such training. However, in view of the significantly increased interest in this training program, the consequent growth in the number of applicants and the limited capacity of DND's Laboratory, the CND at its thirty-first session, felt that a phased decentralization of the basic training activities was necessary. Such decentralization would:

—promote at the regional level law enforcement-supporting expertise in the identification and analysis of material seized from the illicit traffic;

—respond to regional characteristics of the illicit traffic in narcotic and psychotropic drugs by providing technical personnel with the training skills corresponding to the particular needs of the region;

—cover the rapidly increasing need in the Asian, Pacific and Latin American regions for basic training in laboratory techniques;

—increase cost-effectiveness of the United Nations training activities by reducing the costs per head and by focusing training time on skills particularly required in the region.

After careful analysis the Asian and Pacific Region was selected for the first phase of the decentralization process. One training course involving six chemists from four countries was successfully completed in 1986 in Bangkok, Thailand, and a second one is due to begin in that city in September, 1987 in which again six chemists from four countries will participate.

Preparations for the second phase of decentralization have been completed and a training program will be initiated soon in Buenos Aires for the Latin American region.

It is too early to judge whether the decentralized trianing program will be more advantageous or more cost-effective than at headquarters, but it is clear that a careful evaluation will be undertaken in due time to assess that.

Establishment and/or Strengthening of National Laboratories

It is not enough to establish qualified, experienced or trained staff. These staff, in order to fulfill the role expected of them, need the facilities and the tools required for the discharge of their duties.

DND's laboratory has, since 1974, also been assisting, upon request and according to established guidelines, developing countries in regions most affected by the illicit traffic of drugs, in the establishment and/or reinforcement of their national narcotics/forensic laboratories. Such assistance includes the procurement of basic laboratory equipment and material, necessary reference textbooks, handbooks, indexes, encyclopedia and the like, as well as the provision of reference samples so necessary for analytical and research purposes, as well as advice on general safety and security in the laboratory.

It is strongly felt that these national laboratories, with adequate resources, would effectively fulfill important functions such as:

(i) the rapid identification and analysis of substances suspected of being drugs;

(ii) the training of local personnel for this purpose;

(iii) the conduct of scientific investigations and/or research on drugs of abuse.

In responding to requests for technical assistance from Member States in connection with narcotics laboratories, the United Nations has repeatedly indicated the crucial importance of ensuring that available technical skills are commensurate with the choice, acquisition, use and maintenance of available equipment. Experience has also shown that many of the basic skills and equipment needed for a national narcotics laboratory may already exist either, for example, in government laboratories which have been established for other purposes such as public health and drug quality control or in university facilities.

A first step, when considering the establishment or strengthening of national narcotics laboratories is therefore to review existing resources and to consider establishing narcotics laboratories in close proximity to relevant existing facilities, thus avoiding costly duplication of expensive items of equipment and dissipation of technical skills.

For this purpose, a manual was prepared (DND, 1984) to provide practical assistance to national authorities by listing the basic requirements in skills, equipment and reference material which are needed to operate a narcotics laboratory. It may also serve as a guide to national authorities in assessing existing resources in government and university facilities. Not all of the equipment listed is necessarily required in every national narcotics laboratory as requirements may vary, for example, because of local trends in the illicit traffic and the availability of narcotics laboratory facilities on a regional basis.

Preparation of Working Tools and Manuals

It is clear that over the past few years, there has been a considerable increase in the number of substances now scheduled under international control. This increase reflects a rapid diversification of drugs of abuse, the intensification of national regulatory efforts and more and more stringent national legislation and sentencing provisions. At the same time, the seized quantities of drugs already under control, such as the opiates, cocaine and coca paste, cannabis products, amphetamine and related compounds have also shown an alarming and unprecedented increase in certain regions.

Also, owing to the ingenuity of chemists in clandestine laboratories, unexpected new illicit drugs or combinations of drugs appear on the illicit market, requiring rapid and adequate action as well as ingenuity on the part of forensic chemists. The increased number of controlled substances and related legislative provisions places additional pressure on national forensic and narcotic laboratories and their staff. Analysts have to be able to deal with more substances and preparations and to use faster, more accurate and more specific methods for the qualitative identification and quantitative analysis of seized material. This situation presents a challenge not only to national law enforcement authorities, but also to the technical and scientific staff of forensic laboratories. In addition, the international character of drug trafficking requires the rapid exchange of analytical data between laboratories and law enforcement authorities both on the national and the international levels. Development of internationally acceptable methods of testing would contribute greatly to the achievement of these objectives, and this possibility has been under consideration for some time.

At its eighth special session (1984), the Commission on Narcotic Drugs requested the Secretary-General "to investigate the possibility of reaching agreement at the regional and interregional levels on recommended methods of analysis of drugs seized from the illicit traffic." The CND was of the opinion that closer scrutiny and harmonization of the wide variety of analytical methods in use at the national level would not only ease the task of the staff of national institutions, but would also facilitate the exchange of information at regional and interregional levels.

Based upon those considerations, DND's Laboratory, in cooperation with and financial assistance from the Government of the Federal Republic of Germany through the United Nations Fund for Drug Abuse Control (UNFDAC), organized and convened two expert group meetings in Wiesbaden, Federal Republic of Germany in 1985 and Kuala Lumpur, Malaysia in 1986.

The first meeting dealt with methods for the identification and analysis of heroin and cocaine (Expert Group, 1985) and the second meeting dealt with cannabis and amphetamine/methamphetamine (Expert Group, 1986). The established methods recommended by the expert groups appear in four manuals (DND, 1984, 1986, 1987a, 1987b) of which a total of 900 copies have been distributed to laboratories worldwide.

Other meetings planned for 1987 include:

Buenos Aires, Argentina, September 1987 to address new developments in the analysis of cocaine, opium and crude morphine and

Vienna or Brussels in October, 1987 to consider the development of guidelines for the establishment of national testing laboratories to body fluids for dependence-producing drugs under international control based upon critical evaluation of the legal, regulatory, socio-medical, and chemical/biological, technical and financial issues involved.

Prior to submission to laboratories for analysis the trafficked material must be seized and undergo preliminary and presumptive identification. The constantly changing pattern of illicit drug traffic has confronted customs and frontier control officials particularly in developing countries with the difficult and challenging tasks of finding and identifying the drugs being smuggled. The task of identification is especially difficult at remote frontier crossing points which are far away from well-equipped forensic narcotics laboratories.

Recognizing this problem, the Commission on Narcotic Drugs at its twenty-ninth session (1981) recommended, within the long-term strategy and the United Nations basic five-year program of action, that the DND Laboratory should improve methods for the rapid identification of substances seized from the illicit traffic through the use of low cost practical drug identification kits in order to assist law enforcement personnel in their field operations.

Indeed, a State's first line of defense against the illicit traffic is at frontiers, harbors, ports, airports and other entry points. If traffickers and their couriers succeed in passing these points undetected, consignments of drugs are often rapidly broken down into retail quantities, and their removal from the illicit traffic becomes much more difficult. The use of the kits by customs and other frontier control personnel is expected to assist in interdicting illicit traffic and in helping to ensure that the quantities of illicit drugs which enter the territory of the States concerned are kept in check. Also, it was essential that the kits be easy to use and sturdy enough to resist harsh climatic and other conditions which are often a feature of remote frontier crossing points and sea ports where controls must be effected.

With the financial assistance of the Government of Austria through UNFDAC, DND's Laboratory developed low cost drug identification kits for the rapid presumptive identification of drugs seized from the illicit traffic and in the last three years, has distributed over 2,000 such kits to more than 50 countries.

In a recent Expert Group Meeting held in Vienna last May in cooperation with and with the financial assistance from the Government of Austria through UNFDAC, the existing scientific knowledge of color reactions and spot tests for narcotic and psychotropic drugs was reviewed. A selection of the most appropriate tests for field and small-scale laboratory operations was made to cover additional classes of substances brought under international control relatively recently, for example, benzodiazepines. In addition, the group saw fit to consider color reactions for the field identification of certain precursors, including anthranilic acid, ephedrine, norpseudoephedrine, benzyl methyl ketone, lysergic acid and piperidine. The methods recommended by the Expert Group will be included in a working manual to be published in the near future and the new generation of UN-produced drug identification kits will incorporate the recommendations made by the Expert Group.

In response to the General Assembly (1985) and the Economic and Social Council (1985), the Commission on Narcotic Drugs adopted a resolution (1985) requesting the preparation of a draft convention.

This convention is expected to address, *inter alia,* measures to monitor or control specific chemicals, solvents and precursors used in the illegal processing or manufacture of controlled drugs. Article 8 of that Convention would be the relevant provision.

The CND therefore felt that a review of the technical elements involved in the clandestine synthesis of drugs of abuse (e.g. definitions, chemicals required) would be needed to make any sound decision in the future. A similar feeling was expressed at the Meeting of Operational Heads of National Narcotics Law Enforcement Agencies, Far East Region (Honlea, 1985) where "it was agreed that it would be very valuable to develop a comprehensive list of specific precursors, chemicals and solvents".

Aware of the growing concern of the international community and in response to the wishes of the Commission on Narcotic Drugs, the Division of Narcotic Drugs has undertaken to prepare this publication (1987) as a working reference manual making use of valuable reviews supplied by national authorities as well as of available literature. It includes lists of:

(a) essential raw materials and chemicals;

(b) other chemicals (precursors and reagents);

(c) solvents.

These substances are known to have been used in the illicit production (synthesis or extraction) of drugs of abuse. In addition, it provides information on impurities, adulterants/diluents and other compounds known to be present in the final clandestine products. Useful references to the appropriate literature on methods for their identification and analysis are also included.

Because the number and variety of drugs produced clandestinely at present is large and constantly growing, the scope of the manual had to be limited to those substances under international control which are most frequently synthesized or extracted and trafficked clandestinely.

In response to a request of the Commission on Narcotic Drugs and pursuant to the International Drug Abuse Control Strategy, the Division of Narcotic Drugs has published the Multilingual Dictionary of Narcotic Drugs and Psychotropic Substances Under International Control, designed to serve as a reference manual to assist concerned national and international authorities in their drug control activities, particularly those authorities whose tasks have been made difficult by a variety of names for products containing controlled narcotic drugs and psychotropic substances. The languages used are English, French, Russian and Spanish. In addition, the principal names of the drugs in Arabic and Chinese are listed alphabetically in annexes.

The Dictionary includes substances under international control by virtue of the Single Convention on Narcotic Drugs, 1961; the 1972 Protocol Amending the Single Convention; and the Convention on Psychotropic Substances 1971. In addition, the Dictionary provides information received in response to an inquiry sent to all Governments concerning the names used for substances under international control, as well as for preparations containing such substances.

The Dictionary can help to identify controlled narcotic drugs and psychotropic substances among components of pharmaceutical products. A vast and growing number of such pharmaceutical products, under a variety of trade names, is available in legitimate commerce. Unfortunately, many are subject to diversion into the illicit market. In order to counter such diversion of drugs, law enforcement officials should have ready access to a reference publication to identify suspected substances by name.

The Dictionary also identifies many vernacular names that are employed by drug users to describe illicit drugs. The listing of vernacular names will assist drug law enforcement officers in identifying drugs of abuse when such drugs are being described by the individuals dealing with them illegally.

The Dictionary is an additional working tool that is expected to be particularly valuable for officials of customs and related services involved in the fight against drug trafficking. Similarly, officials concerned with monitoring legitimate commerce need to have quick access to the information on the nature of substances that are being traded in order to establish whether trade in these substances is in conformity with national legislation and with the international drug control treaties. It is hoped that the Dictionary will help in performing these duties.

The Multilingual Dictionary will be updated, as necessary, to provide new information on the substances dealt with therein and on those substances newly brought under international control.

Reference Samples of Substances Under International Control

Increasing legal requirements, more stringent national legislation and sentencing provisions worldwide put increasing pressure on responsible national forensic and narcotic laboratories and their chemists. They are increasingly required to provide more specific and accurate results to courts of law in identifying and quantitating seized controlled substances. This is especially important for drugs most commonly encountered in illicit traffic such as heroin, opium, cocaine, cannabis products and amphetamines.

In view of this trend, the Commission on Narcotic Drugs at its eighth special session stressed the important role of the DND Laboratory in providing national laboratories with reference samples and in the "exchange of appropriate information and analytical data with national and regional narcotics and forensic laboratories on identification and analysis relating to reference samples." The Commission, at its thirty-first session (1985), recommended that this activity should be vigorously intensified.

In pursuance of those recommendations the DND Laboratory has intensified its efforts over the last years to collect and distribute reference samples of drugs under international control. Its collection now also includes samples of controlled substance analogues, for example, MDA, MDMA, MMDA and other amphetamine-like substances. Certain other analogues not yet under international control including those of fentanyl are also in the reference collection thanks to the DEA and the Royal Canadian Mounted Police. During 1986 alone over 400 reference samples were distributed to 44 laboratories in 25 countries free-of-charge. These samples are suitable for the routine identification and analysis of seized drugs but do not at present have authentication and detailed quality specifications. Authentication and establishment of quality specification data are being performed in the DND Laboratory and in close collaboration with national laboratories, a collaboration with national laboratories, a collaboration which the DND highly values.

It must be pointed out that authenticated samples with quality guarantee of some of the substances under international control are at present available at some commercial distributors but the commercial products are exceedingly expensive and those distribution programs do not cover the entire range of substances that are needed (opioids, cannabinoids, coca-products, amphetamines). As a result, those samples are not accessible to most narcotics and forensic laboratories, particularly in developing countries. There is an urgent worldwide need for such materials to be distributed free-of-charge as part of the assistance and collaborative programs.

Reference Collection

The Reference Literature Collection which was originally established as a source of specialized technical and scientific information is being further developed into a modern information center, presently covering the broad area of international drug control.

This repository of information is now, in addition to its traditional tasks, actively involved in the collection and dissemination of information on new illicit drugs (designer drugs) as well as new techniques related to the processing and manufacture of new forms of traditional drugs (e.g. "crack", black tar heroin). Further, as an integral part of the control techniques, laboratory methods and other relevant material including the production of specific technical notes are part of this collection. This information is distributed in the form of specific information kits to requesting scientific institutions.

The constant increase and changing pattern in the illicit production, trafficking, transiting and abuse of drugs require intensified efforts to promote international cooperation in combatting illicit drug traffic and drug abuse which present an ever increasing threat to the international community.

In the complex worldwide effort to combat the illicit traffic in narcotic drugs, national narcotics laboratories have an important role to play, and the Division of Narcotic Drugs, through its narcotics laboratory, fulfills a clearing house function and also helps to establish internationally accepted norms and guidelines for consistent action in assisting national laboratories to carry out their difficult tasks.

It should be emphasized that the ongoing action-oriented activities of the Laboratory just described constitute the core of a technical assistance program to assist Member States with limited technical and scientific expertise and resources. These activities have been recently conceptually reformulated and executed by the permanent staff of the Laboratory, drawing, as required, on available know-how from collaborative institutions and scientists in developed Member States. The Division considers such collaboration which promotes international participation and solidarity very important in ensuring continuous availability of up-to-date knowledge for transfer of skill and technology to countries in need.

Bibliography

Commission on Narcotic Drugs, Report on the eighth special session, New York, United Nations (1984);

Commission on Narcotic Drugs, Report on the twenty-ninth session, New York, United Nations (1981);

Commission on Narcotic Drugs, Report on the thirty-first session, New York, United Nations (1985);

Division of Narcotic Drugs, recommended methods for testing heroin, Vienna, United Nations (1986);

Division of Narcotic Drugs, recommended methods for testing cocaine, Vienna, United Nations (1986);

Division of Narcotic Drugs, recommended methods for testing cannabis, Vienna, United Nations (1987);

Division of Narcotic Drugs, recommended methods for testing amphetamine and methamphetamine, Vienna, United Nations (1987);

Division of Narcotic Drugs, Clandestine manufacture of substances under International Control, Vienna, United Nations (1987);

Division of Narcotic Drugs, Multilingual Dictionary of Narcotic Drugs and Psychotropic Substances under International Control, New York, United Nations (1983);

Division of Narcotic Drugs, Staff Skills and Basic Equipment for Narcotics Laboratories, Vienna, United Nations (1984);

Economic and Social Council, Official Records, New York, United Nations (1985);

Expert Group Meeting on Cocaine and Heroin Analysis and Recommended Methods of Testing, Report, Vienna, United Nations (1985);

Expert Group Meeting on Recommended Methods for Testing Cannabis and Amphetamine/Methamphetamine Analysis, Report, Vienna, United Nations (1986);

General Assembly, Resolutions and Decisions, New York, United Nations (1985);

HONLEA, Far East Region, Report, Colombo (1985).

Synthesis and Evaluation of Amphetamine Analogues

Richard A. Glennon Ph.D.

Introduction

The basic structural unit, or parent structure, of amphetamine-related compounds is phenethylamine (i.e., 1-amino-2-phenylethane, benzeneethaneamine). Substitution of a methyl group on the alpha carbon of phenethylamine results in phenylisopropylamine (i.e., 2-phenyl-1-aminopropane, amphetamine; see Scheme 1). A great variety of methods are available for the synthesis of these phenalkylamines and their substituted derivatives. What follows is not an exhaustive compilation of these methods but is, rather, a discussion of the various types of reactions that have been used. The reactions are classified on the basis of the starting materials employed; this classification is arbitrary and is meant to reflect the diversity of starting materials that can be used. Although not all of these methods have been applied to the clandestine synthesis of amphetamine-related drugs, they are certainly available to anyone who reads the literature. Some of these methods, including some of the more sophisticated syntheses, have also been described in various popular "underground" publications such as "Drug Manufacturing for Fun and Profit" (Stone Kingdom) and "Psychedelic Chemistry" (Rip Off Press). The methods described are for the synthesis of racemic mixtures; however, many of these syntheses can be modified for the preparation of optically active materials, or optically active products can be obtained by resolution of the racemates. For a discussion of optically active amphetamine-related agents, see a review by Glennon (1984).

Following the section on synthesis, the discriminative stimulus properties of selected phenalkylamines will be discussed. Using animals trained to discriminate either (+)-amphetamine or DOM from saline, tests of stimulus generalization have allowed the classification of these agents as either amphetamine-like or DOM (4-methyl-2,5-dimethoxyamphetamine)-like.

Synthesis of Amphetamine Analogues

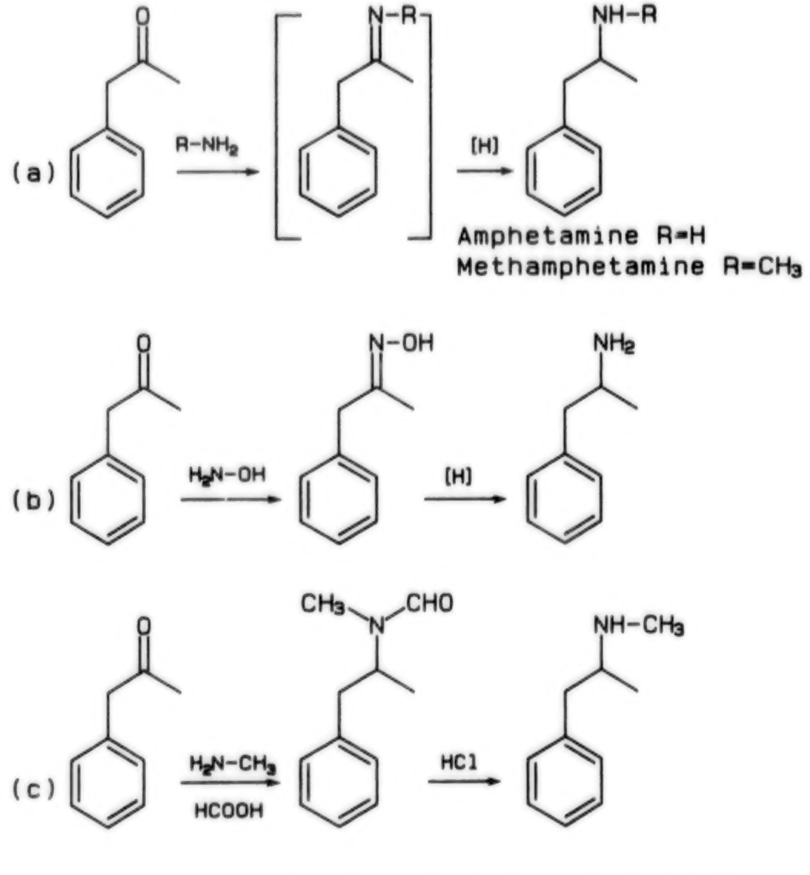
The most common methods of synthesis are via amination of phenylpropanones and via the Knoevenagel reaction using benzaldehyde derivatives. The former method is used primarily, though certainly not exclusively, for the synthesis of amphetamine and methamphetamine whereas the latter method is of general applicability and is used more for the synthesis of phenethylamines and phenylisopropylamines bearing aromatic substituents.

Synthesis via phenyl-2-propanones

As mentioned above, the phenylpropanone method is used primarily for the synthesis of amphetamine, methamphetamine, and a few other compounds, depending on the commercial availability of the requisite propanones. However, with the Schedule II control of phenylpropanone (phenyl-2-propanone, phenylactone, methyl benzyl ketone, P2P) in the Controlled Substances Act in 1980 has come an increased interest in the synthesis of this precursor.

Scheme 1

Synthesis of amphetamine and methamphetamine using the phenylpropanone method.



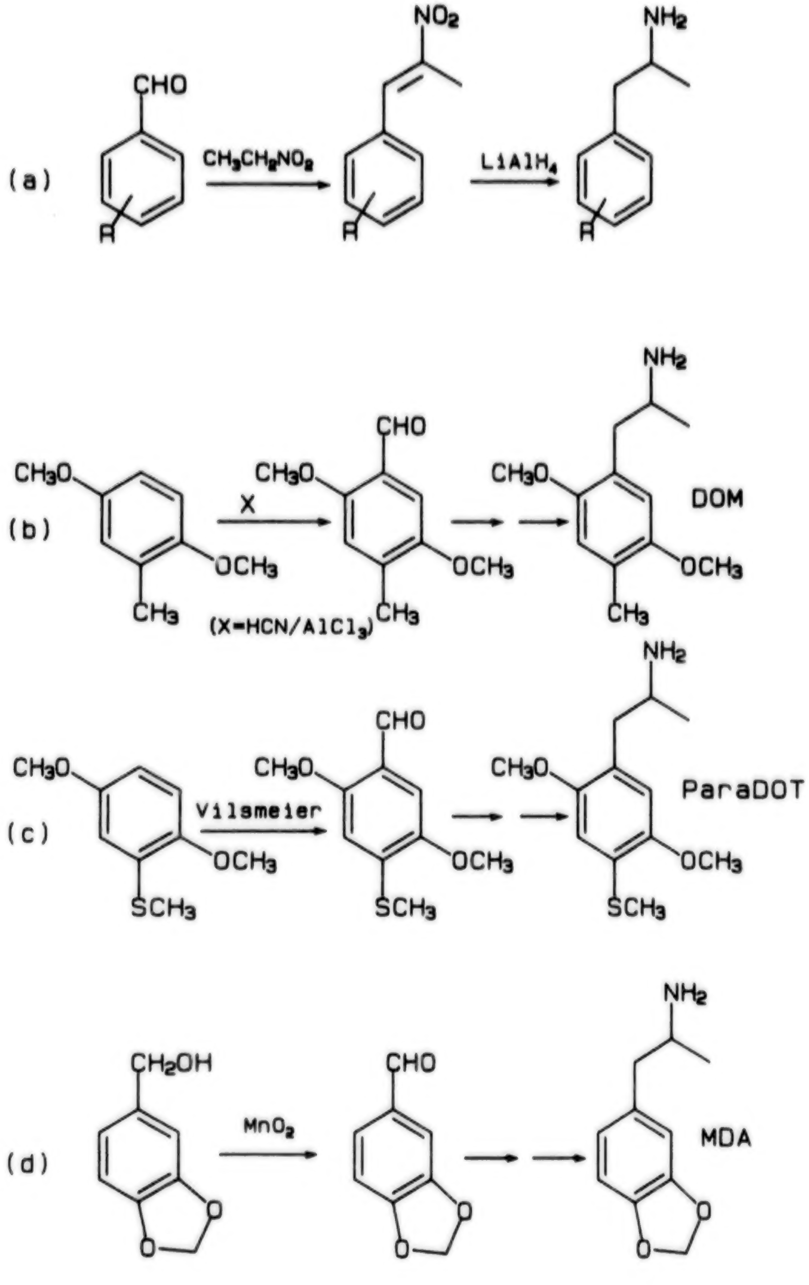
There are several variations on the synthesis of amphetamine-related agents from phenylpropanone (Scheme 1). Condensation of phenylpropanone with ammonia (or with methylamine) under reducing conditions provides amphetamine (or methamphetamine) via the imine intermediate (Scheme 1a). Alternatively, the oxime formed from the reaction of phenylpropanone and hydroxylamine can be reduced by any one of several methods to afford amphetamine (Scheme 1b). A third method for the synthesis of amphetamine involves the Leuckart reaction (i.e., reaction of phenylpropanone with either formamide or ammonium formate). Use of N-methylformamide or a mixture of methylamine and formic acid provides methamphetamine (Scheme 1c). Sinnema and Verweij (1981) have reviewed the phenylpropanone method and some of the synthetic impurities that can be formed in the illicit preparation of amphetamine and methamphetamine. Although less common, this general method has been used to synthesize, for example, 2,4,5-trimethoxyamphetamine (2,4,5-TMA) via the oxime, (Stone, 1963), and MDA (3,4-methylenedioxyamphetamine (i.e., the Love Drug) (Fujisawa *et al.*, 1956) and MDMA (3,4-methylenedioxymethamphetamine) (i.e., Ecstasy, Adam) (Braun *et al.*, 1980a) via the Leuckart reaction. Aryl-substituted phenylpropanones can be readily prepared by catalytic reduction of aryl-substituted 2-nitro-1-phenylpropenes; thus, entry into a wide variety of substituted derivatives is possible. However, because it is usually more convenient to reduce the nitropropenes directly to their corresponding amphetamine-related derivatives with metal hydride reducing agents, this route has not been as attractive as it might appear. Nevertheless, this route is important for the synthesis of optically-active amphetamine analogues (Nichols *et al.*, 1973).

Synthesis via the Knoevenagel Reaction

If the phenylpropanone method is the most common synthesis of amphetamine-related agents, the Knoevenagel reaction (or the nitroalkane method) (Scheme 2) is the most general (e.g., see Ho *et al.*, 1970; Aldous *et al.*, 1974). This method involves the condensation of an appropriately substituted benzaldehyde with a nitroalkane (usually nitromethane for the synthesis of phenethylamine derivatives or nitroethane for the synthesis of phenylisopropylamine or amphetamine derivatives) to form a 2-nitro-1-phenylpropene which can then be reduced by a metal hydride reducing agent (Scheme 2a). There are usually only two limitations to the reaction: (a) the availability of the requisite benzaldehyde and (b) the nature of the substituents. Many of the benzaldehydes are available either synthetically or from commercial sources. Lithium aluminum hydride is usually used as the reducing agent and most substituents commonly found in behaviorally-active amphetamine analogues are generally stable to this reagent. The one major exception is halogen; when halogen substituent (e.g. bromo, iodo, chloro) is present, lithium aluminum hydride reduction will result in very low yields due to dehalogenation (e.g., see Barfknecht and Nichols, 1971); in fact, the dehalogenated product may

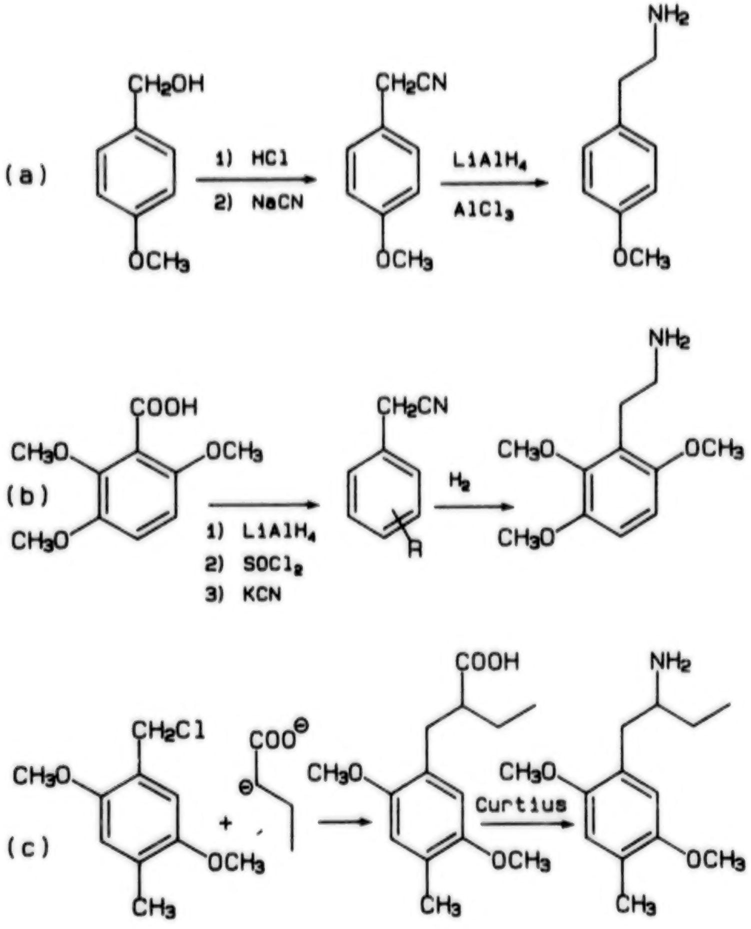
Scheme 2

Synthesis of phenylisopropylamines using the Knoevenagel reaction.



Scheme 3

Synthesis of phenalkylamines from (a) benzyl alcohols, (b) benzoic acids, and (c) benzyl halides.

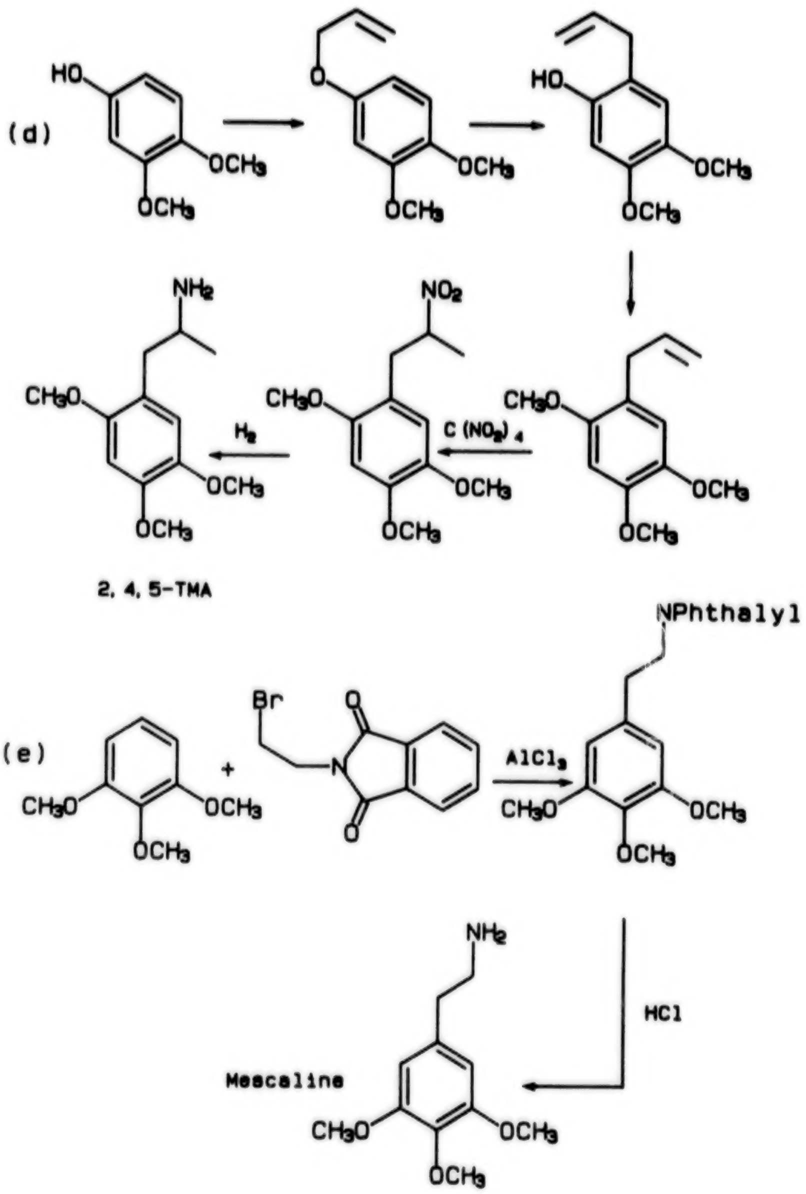


be the only product isolated from the reaction. Dehalogenation can normally be obviated by using alane (AlH_3) (e.g. see Glennon *et al.*, 1986a) or borane (BH_3) (plus a catalytic amount of sodium borohydride) (Mourad *et al.*, 1984) as the reducing agent.

Several methods are available for the facile preparation of the requisite benzaldehydes. The most common of these are the formylation of substituted benzenes by, for example, the Gattermann reaction (e.g. Scheme 2b; Sayish *et al.*, 1964) or the Vilsmeier reaction (e.g. Scheme 2c; Jacob *et al.*, 1977) and oxidation of substituted benzyl alcohols (e.g. Scheme 2d; Nichols and Kostuba, 1979).

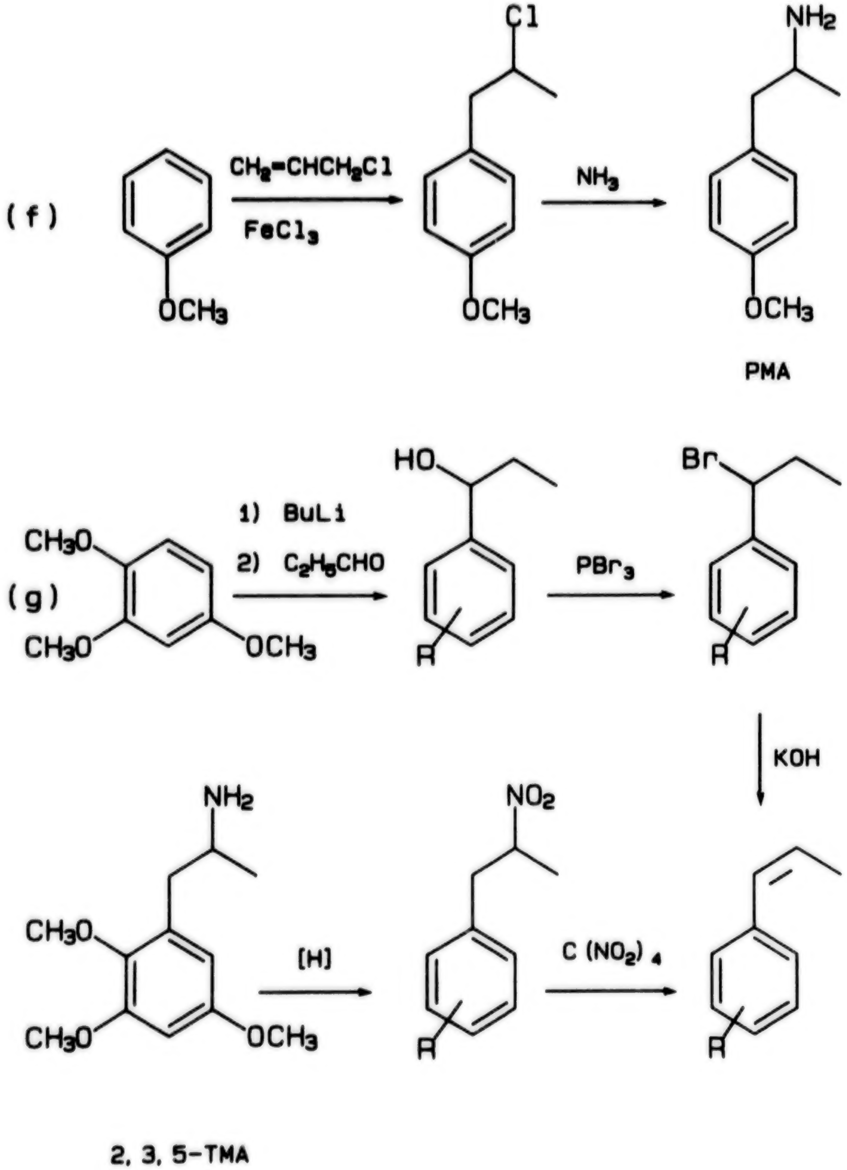
Scheme 3 (contd.)

Synthesis of phenalkylamines from benzene derivatives.



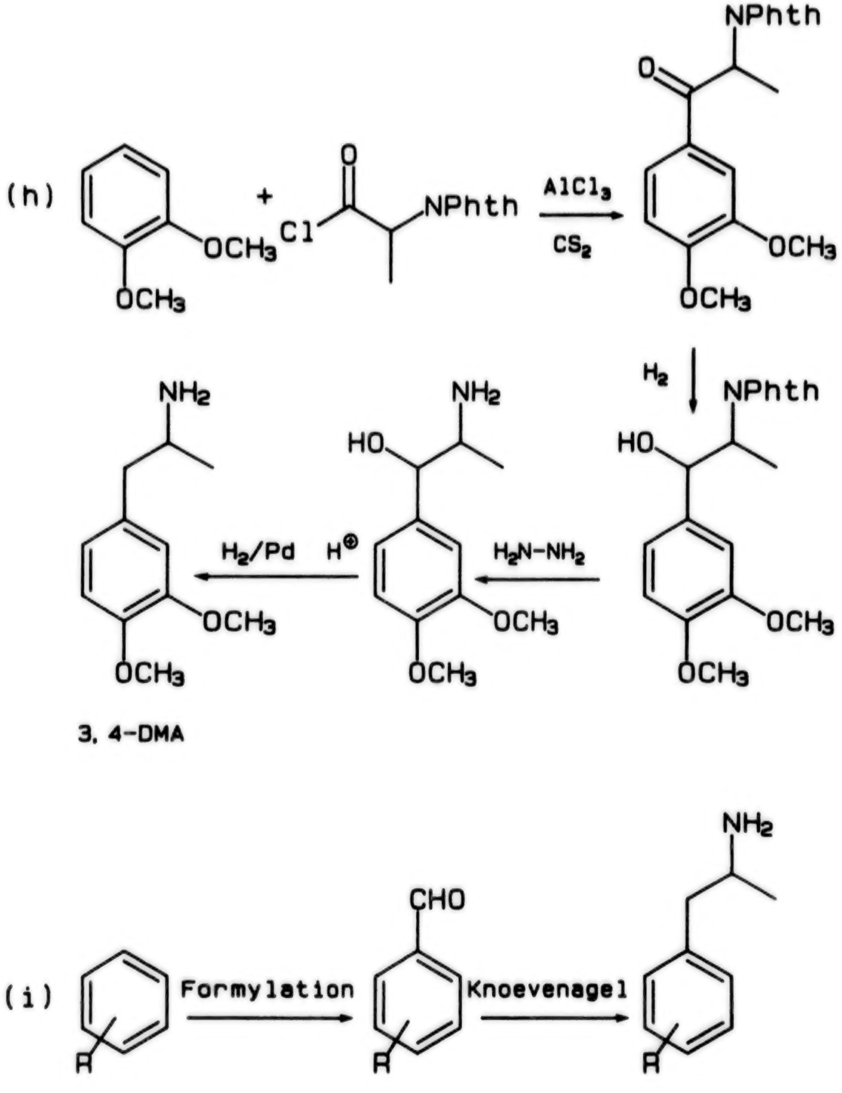
Scheme 3 (contd.)

Synthesis of phenalkylamines from benzene derivatives.



Scheme 3 (contd.)

Synthesis of phenalkylamines from benzene derivatives.



Synthesis from Other Aromatic Precursors

From benzyl alcohols. In addition to oxidation of benzyl alcohols to their corresponding aldehydes (for use in the Knoevenagel reaction), benzyl alcohols can be converted to their benzyl halides, reacted with cyanide, and the resulting phenylacetonitrile reduced to the corresponding amine. This method has found some application in the synthesis of phenethylamine derivatives such as, for example, mescaline and (as shown in Scheme 3a) for 4-methoxyphenethylamine (Kiefer, 1972).

From benzoic acids. Reduction of benzoic acids affords benzyl alcohols. These benzyl alcohols can be used in reactions similar to that described above; an example of this approach for the synthesis of 2,3,6-trimethoxyphenethylamine (Benington and Morin, 1971) is shown in Scheme 3b.

From benzyl halides. Benzyl halides were used as intermediates in the above two reactions. However, Scheme 3c shows the reaction of a benzyl halide with the anion generated from butyric acid to yield an acid derivative that was subsequently converted to an amine by Curtius rearrangement (Standridge *et al.*, 1976). The last step of this reaction, the Curtius rearrangement, had been used earlier by Schrecher and Hartwell (1957) for the synthesis of 3,4-dimethoxyamphetamine (3,4-DMA) from 2-(3,4-dimethoxyphenyl)propionic acid.

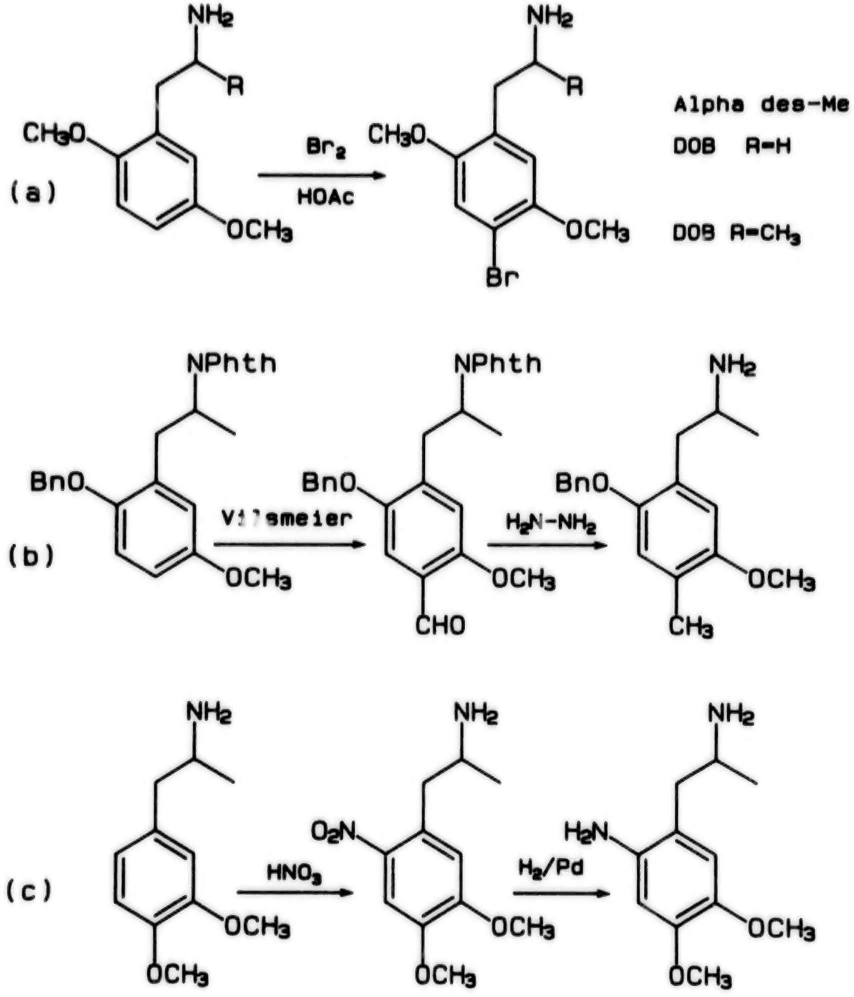
From phenols. This interesting reaction has been used several times to prepare 2-methoxy-substituted derivatives of phenalkylamines. Alkylation of the appropriately substituted phenol with an allyl halide followed by Claisen rearrangement provides a 3-aryl-1-propene. Nitration of this propene with tetranitromethane affords the desired amine after alkylation of the phenolic hydroxyl group and reduction. Shulgin (1966) has used this method for the synthesis of, for example, 2,4,5-TMA (Scheme 3d).

From substituted benzenes. Most of these reactions involve Friedel-Crafts alkylation or acylation reactions. Alkylation of 3,4,5-trimethoxybenzene with N-(2-bromoethyl)phthalimide in the presence of aluminum chloride ($AlCl_3$) followed by removal of the phthalimido protecting group by hydrolysis, results in mescaline (Rabusic and Gregor, 1968). Treatment of 4-substituted benzenes (e.g. 4-methoxybenzene) with allyl chloride and ferric chloride ($FeCl_3$) followed by amination with ammonia gives the corresponding phenylisopropylamine (Scheme 3f) (Patrick *et al.*, 1946). Shulgin (1966) has reported that reaction of 1,2,4-trimethoxybenzene with butyl lithium and propionaldehyde yields 1-hydroxy-1-(2,3,5-trimethoxyphenyl)propane; treatment of this alcohol with phosphorus bromide (PBr_3) followed by dehydrohalogenation to the propene, nitration of the propene with tetranitromethane, and reduction, affords 2,3,5-TMA (Scheme 3g). Beckett and co-workers (1965) have prepared 3,4-DMA by Friedel-Crafts acylation of 1,2-dimethoxybenzene with N-[1-(chlorocarbonyl)ethyl]phthalimide followed by reduction and deprotection of the terminal amine (Scheme 3h). Perhaps one of the major uses of such precursors is for the preparation of benzaldehydes as starting materials for the Knoevenagel reaction; the most common method of formylation is the Vilsmeier reaction (Scheme 3i).

From propiophenones (1-phenylpropanones). This method has been principally used for the synthesis of phenalkylamine derivatives bearing a benzylic hydroxyl group (e.g. norephedrine-type compounds) but is amenable to the synthesis of amphetamine analogues. Nitrosation of 1-phen-

Scheme 4

Synthesis of phenalkylamines from pre-formed phenalkylamines.



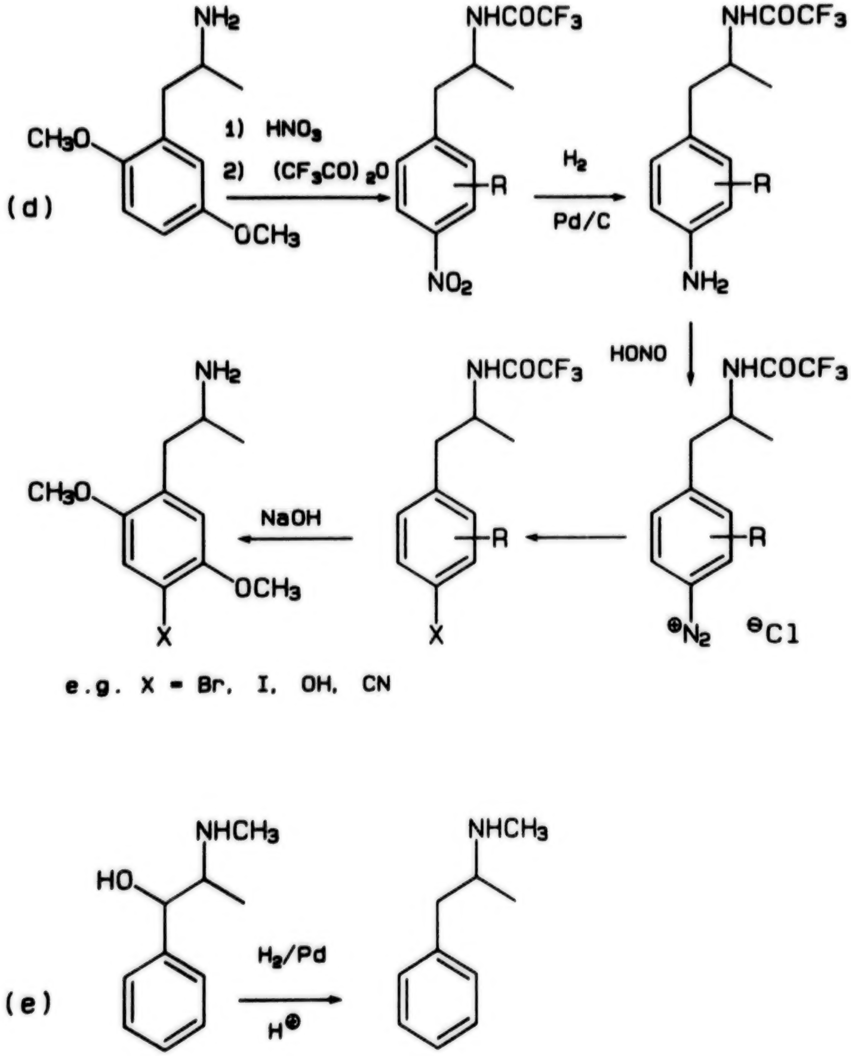
ylpropanones followed by reduction provides hydroxyphenalkylamines (i.e., phenylpropanolamines) (Hartung *et al.*, 1931). The hydroxyl group can be fairly readily removed by hydrogenolysis (see next section).

Synthesis from Pre-formed Phenalkylamines

Once an appropriate phenalkylamine has been synthesized, it can be used as starting material for subsequent reactions. For example, Shulgin and Carter (1975) have brominated 2,5-dimethoxyphenethylamine using bromine in acetic acid to afford 4-bromo-2,5-dimethoxyphenethylamine

Scheme 4 (contd.)

Synthesis of phenalkylamines from pre-formed phenalkylamines.



(also known as 2-CB; i.e., the phenethylamine counterpart of 4-bromo-2,5-dimethoxyamphetamine (DOB)) (Scheme 4a). Likewise, DOB has been prepared by the bromination of 2,5-DMA (Scheme 4a) (Glennon *et al.,* 1986a) and direct bromination of 2,4-DMA provides 5-bromo-2,4-DMA (Sepulveda *et al.,* 1972). Zwieg and Castagnoli (1977) have prepared the 2-hydroxy analogue of DOM by formylation of N-phthalimido-protected 1-(2-benzyloxy-5-methoxyphenyl)-2-aminopropane followed by deprotection (Scheme 4b). 2-Amino-4,5-DMA has been prepared by nitration of 3,4-DMA followed by reduction (Scheme 4c) (Stone, 1963). Nitration of 2,5-DMA occurs at the 4-position. Glennon and co-workers have taken advantage of this reaction to prepare the 4-amino derivative (via reduction of the nitro group) which was used in the Sandmeyer reaction; in this way, it was possible to prepare a variety of derivatives including DOB and DOI (4-iodo-2,5-dimethoxyamphetamine) (Scheme 4d). One of the methods for the synthesis of methamphetamine involves catalytic hydrogenolysis of ephedrine in the presence of acid (Scheme 4e); the hydroxyl group of ephedrine may first be converted to a chloro group by reaction with thionyl chloride to facilitate the reaction (Allen and Kiser, 1987).

Synthesis of N-Substituted Phenalkylamines

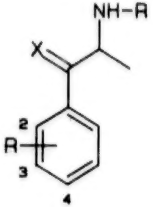
With the exception of methamphetamine, N-substituted phenalkylamines (i.e., phenalkylamines or amphetamine derivatives bearing a substituent on the terminal amine function) have received relatively little attention from a pharmacological standpoint. The recent popularity of MDMA has, to some extent, kindled a renewed interest in N-alkyl analogues. Recent findings from our laboratory (e.g. see Table 1) as well as reports by several others (e.g. Benington *et al.*, 1965; Gorrod and Jenner, 1975; Braun *et al.*, 1980b) suggest that a re-examination of N-hydroxyl (N-OH) phenalkylamines might also be worthwhile. Because many (if not most) of these N-substituted agents are not currently controlled, they may constitute the next wave of controlled substance analogues that might appear on the illicit market.

N-Alkyl derivatives. N-Methyl phenalkylamines are commonly prepared by the phenylpropanone method; the synthesis of methamphetamine, for example, is shown in Scheme 1. Aryl-substituted phenalkylamines can also be prepared by this method depending upon the availability of the phenylpropanone precursors. Some of the other methods described above can also be used; thus, in many of the procedures requiring ammonia, substitution of the ammonia by an alkylamine will often afford the N-alkyl phenalkylamine.

The most general method for the preparation of N-alkyl phenalkylamines is the indirect alkylation of preformed phenalkylamines; for example, acylation of the phenalkylamine and hydride reduction of the subsequent acyl analogue (i.e., formamide, amide, carbamate) provides the desired N-alkyl derivatives (Scheme 5a). Bailey and co-workers (1975), Clark (1984), and Glennon and co-workers (1987b) have prepared a number of N-methyl phenalkylamines by reduction of either the N-formyl (formamide) or N-carboethoxy (carbamate) derivatives. Six different methods have been used to prepare the N-methyl analogue of MDA (i.e., MDMA); these methods have been reviewed by Shulgin (1986). Larger alkyl homologues can be prepared in similar fashion; for example,

Table 1

Some agents to which the (+) amphetamine-stimulus generalizes*

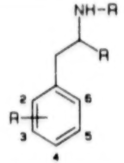


Agent	R_2	R_3	R_4	R′	X	ED50 mg/kg	ED50 umoles/kg
AMPH	H	H	H	H	H2	0.62	3.6
S(+)AMPH	H	H	H	H	H2	0.42	1.8
R(−)AMPH	H	H	H	H	H2	1.23	5.3
OMA	OCH_3	H	H	H	H2	7.82	38.7
MMA	H	OCH_3	H	H	H2	3.44	17.0
PMA	H	H	OCH_3	H	H2	1.91	9.5
N-Me AMPH	H	H	H	CH_3	H2	0.71	3.8
S(+)N-Me AMPH	H	H	H	CH_3	H2	0.40	2.1
S(+)N-Et AMPH	H	H	H	C_2H_5	H2	0.87	4.3
N-OH AMPH	H	H	H	OH	H2	0.38	1.0
MDA	H	$-OCH_2O-$	$-OCH_2O-$	H	H2	2.29	10.6
S(+)MDA	H	$-OCH_2O-$	$-OCH_2O-$	H	H2	0.90	4.2
MDMA	H	$-OCH_2O-$	$-OCH_2O-$	CH_3	H2	1.64	7.1
Cathinone	H	H	H	H	O	0.72	3.8
S(−)Cathinone	H	H	H	H	O	0.34	1.8
R(+) Cathinone	H	H	H	H	O	4.41	23.4
Methcathinone	H	H	H	CH_3	O	0.37	1.8
Propylhexedrine						2.18	12.3
Fenethylline						4.74	12.5

*All agents are racemates unless otherwise noted.

Table 2

Some agents to which the (+) amphetamine-stimulus did not generalize

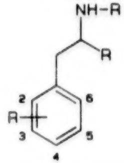


Agent	R_2	R_3	R_4	R_5	R_6	R′	R″	Note*
PEA	H	H	H	H	H	H	H	
4-OH AMPH	H	H	OH	H	H	CH_3	H	(10)
2,3-DMA	OCH_3	OCH_3	H	H	H	CH_3	H	
2,4-DMA	OCH_3	H	OCH_3	H	H	CH_3	H	
N-Me 2,4-DMA	OCH_3	H	OCH_3	H	H	CH_3	CH_3	(10)
2,5-DMA	OCH_3	H	H	OCH_3	H	CH_3	H	
2,5-DMA, S(+)	OCH_3	H	H	OCH_3	H	CH_3	H	(9)
N-Me 2,5-DMA	OCH_3	H	H	OCH_3	H	CH_3	CH_3	
2,6-DMA	OCH_3	H	H	H	OCH_3	CH_3	H	(15)
3,4-DMA	H	OCH_3	OCH_3	H	H	CH_3	H	
N-Me 3,4-DMA	H	OCH_3	OCH_3	H	H	CH_3	CH_3	
2,3-MDA	OCH_3	$-OCH_2O-$	H	H	H	CH_3	H	
HPA	H	$-OCH_2O-$	$-OCH_2O-$	H	H	H		
MDA, R(−)	H	$-OCH_2O-$	$-OCH_2O-$	H	CH_3	H		
MDE	H	$-OCH_2O-$	$-OCH_2O-$	H	CH_3	C_2H_5		
MDE, S(+)	H	$-OCH_2O-$	$-OCH_2O-$	H	H	CH_3	C_2H_5	
MDE, R(−)	H	$-OCH_2O-$	$-OCH_2O-$	H	H	CH_3	C_2H_5	
N-OH MDA	H	$-OCH_2O-$	$-OCH_2O-$	H	H	CH_3	OH	
3,5-DMA	H	OCH_3	H	OCH_3	H	CH_3	CH_3	(7)
2,3,4-TMA	OCH_3	OCH_3	OCH_3	H	H	CH_3	H	
2,3,5-TMA	OCH_3	OCH_3	H	OCH_3	H	CH_3	H	
2,4,5-TMA	OCH_3	H	OCH_3	OCH_3	H	CH_3	H	
N-Me 2,4,5-TMA	OCH_3	H	OCH_3	OCH_3	H	CH_3	CH_3	(10)
2,4,6-TMA	OCH_3	H	OCH_3	H	OCH_3	CH_3	H	
3,4,5-TMA	H	OCH_3	OCH_3	OCH_3	H	CH_3	H	
N-Me 3,4,5-TMA	H	OCH_3	OCH_3	OCH_3	H	CH_3	CH_3	
2-OMe MDA	OCH_3	H	$-OCH_2O-$	$-OCH_2O-$	H	CH_3	H	
N-Me 2-OMe MDA	OCH_3	H	$-OCH_2O-$	$-OCH_2O-$	H	CH_3	H	(10)
Mefenorex	H	H	H	H	H	CH_3	$CH_2CH_2CH_2Cl$	

*Note: Doses of each agent were evaluated until either stimulus generalization occurred (in which case, the data are reported in Table 1) or until disruption of behavior (i.e., no responding) was evident. In several instances, the highest dose of an agent resulted in saline-appropriate responding and higher doses were not evaluated; in these cases, the highest dose tested (mg/kg) is reported in parenthesis.

Table 3

Some agents to which the DOM-stimulus generalizes.*



Agent	R_2	R_3	R_4	R_5	R_6	R'	R''	ED50 (umoles/kg)
2,4-DMA	OCH_3	H	OCH_3	H	H	CH_3	H	21.0
2,5-DMA	OCH_3	H	H	OCH_3	H	CH_3	H	23.8
2,5-DMA, R(−)	OCH_3	H	H	OCH_3	H	CH_3	H	14.0
2,3,4,-TMA	OCH_3	OCH_3	OCH_3	H	H	CH_3	H	29.8
2,3,5-TMA	OCH_3	OCH_3	H	OCH_3	H	CH_3	H	63.0
2,4,5-TMA	OCH_3	H	OCH_3	OCH_3	H	CH_3	H	13.7
2,4,6-TMA	OCH_3	H	OCH_3	H	OCH_3	CH_3	H	13.9
3,4,5-TMA	H	OCH_3	OCH_3	OCH_3	H	CH_3	H	24.2
Mescaline	H	OCH_3	OCH_3	OCH_3	H	H	H	67.1
DOM	OCH_3	H	CH_3	OCH_3	H	CH_3	H	1.8
DOM, R(−)	OCH_3	H	CH_3	OCH_3	H	CH_3	H	0.9
DOM, S(+)	OCH_3	H	CH_3	OCH_3	H	CH_3	H	6.9
des Me DOM	OCH_3	H	CH_3	OCH_3	H	H	H	5.6
N-Me DOM	OCH_3	H	CH_3	OCH_3	H	CH_3	CH_3	15.3
N-Me DOM R(−)	OCH_3	H	CH_3	OCH_3	H	CH_3	CH_3	10.0
DOET	OCH_3	H	C_2H_5	OCH_3	H	CH_3	H	0.9
DOET, R(−)	OCH_3	H	C_2H_5	OCH_3	H	CH_3	H	0.3
DOET, S(+)	OCH_3	H	C_2H_5	OCH_3	H	CH_3	H	3.3
DOPR	OCH_3	H	nC_3H_7	OCH_3	H	CH_3	H	0.6
DOIP	OCH_3	H	iC_3H_7	OCH_3	H	CH_3	H	2.9
DOBU	OCH_3	H	nC_4H_9	OCH_3	H	CH_3	H	3.2
DOF	OCH_3	H	F	OCH_3	H	CH_3	H	5.8
DOC	OCH_3	H	Cl	OCH_3	H	CH_3	H	1.2
DOB	OCH_3	H	Br	OCH_3	H	CH_3	H	0.6
DOB, R(−)	OCH_3	H	Br	OCH_3	H	CH_3	H	0.3
DOB, S(+)	OCH_3	H	Br	OCH_3	H	CH_3	H	2.6
N-Me DOB	OCH_3	H	Br	OCH_3	H	CH_3	CH_3	2.5
N-nPr DOB	OCH_3	H	Br	OCH_3	H	CH_3	nC_3H_7	13.4
des Me DOB	OCH_3	H	Br	OCH_3	H	H	H	2.2
2-OH DOB	OH	H	Br	OCH_3	H	CH_3	H	0.6
DOI	OCH_3	H	I	OCH_3	H	CH_3	H	1.2
DOI, R(−)	OCH_3	H	I	OCH_3	H	CH_3	H	0.7
DOI, S(+)	OCH_3	H	I	OCH_3	H	CH_3	H	2.6
DON	OCH_3	H	NO_2	OCH_3	H	CH_3	H	2.7
MDA	H	$-OCH_2O-$	$-OCH_2O-$	H	H	CH_3	H	7.8
MDA, R(−)	H	$-OCH_2O-$	$-OCH_2O-$	H	H	CH_3	H	3.8
2-OMe MDA	OCH_3	H	$-OCH_2O-$	$-OCH_2O-$	H	CH_3	H	13.7

*Note: With the exception of racemic MDA, none of the agents to which the (+)amphetamine-stimulus generalized resulted in stimulus generalization in the DOM-trained animals. Other agents to which the DOM-stimulus did not generalize include: MDMA, R(−)MDMA, S(+)MDMA, MDE (the ethyl homolog of MDMA), R(−)MDE, S(+)MDE, N-OH MDA, HPA, cathinone, R(+)cathinone, S(−)cathinone, (+)norpseudoephedrine (cathine), 2,3,-DMA, 2,6-DMA, 3,4-DMA, 3,5-DMA, DOTB, and DOAM.

see Braun and co-workers (1980a) for the synthesis of a homologous series of N-alkyl analogues of MDA. Other methods that have been employed include tosylate displacement (of 1-phenyl-2-propanol tosylates) by alkylamines, direct alkylation of phenalkylamines, and reduction of imines (formed from the reaction of phenalkylamines and carbonyl compounds). Schaeffer and co-workers (1975) have used nearly all of the possible methods to prepare a wide variety of N-alkyl analogues of amphetamine.

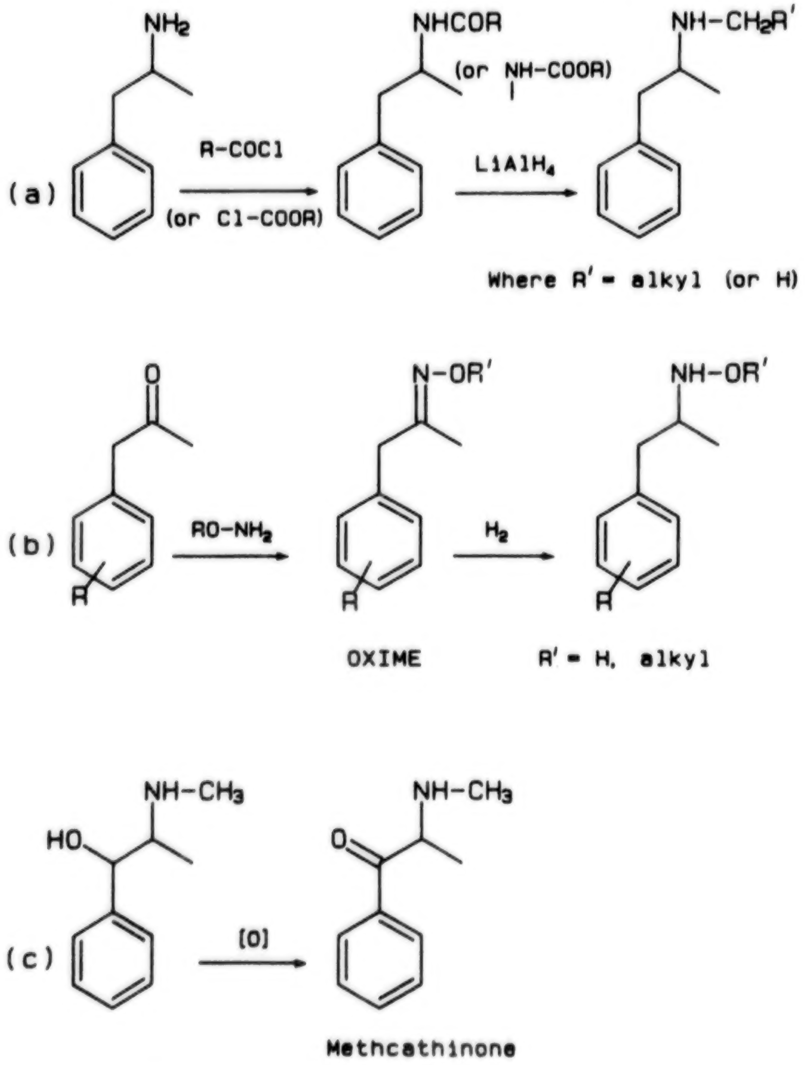
The presence of a carbonyl oxygen on the benzylic carbon atom of amphetamine seems to have little effect on amphetamine-like activity, compare the activity of amphetamine and its benzylic carbonyl derivative cathinone. N-Methylcathinone (methcathinone) was recently prepared by the chromic acid oxidation of ephedrine (Scheme 5c) (Glennon *et al.*, 1987b).

N-Hydroxy derivatives. Reaction of phenylpropanone with hydroxylamine (or with an O-alkyl hydroxylamine) affords the corresponding oxime; N–OH (or N–OR, where R = alkyl) derivatives are obtained upon reduction of these oximes (Scheme 5b) (e.g. see Coutts and Malicky, 1974). The N–OH derivative of amphetamine can be prepared by lithium aluminum hydride reduction (reverse addition) of 2-nitro-1-phenylpropene; partial reduction affords a mixture of the oxime and the N–OH derivative and extended reduction times result in the isolation of amphetamine (Gilsdorf and Nord, 1952). Gal and co-workers (1975) have prepared the N–OH analogue of DOM in a stepwise manner by reducing the nitropropene to a nitropropane with sodium borohydride, followed by reduction of the nitro group. Major and Ohly (1961) and Benington and co-workers (1965) have prepared and examined the pharmacological activity of a number of N–OH and N–OR phenalkylamine derivatives. Braun and co-workers (1980a) have prepared and investigated the N–OH and N–OMe derivatives of MDA (i.e., N–OH MDA and N–OMe MDA).

Cyclic N-substituted derivatives. Another category of N-substituted phenalkylamine derivatives is that in which the N-substituent is cyclized to form a ring with the side chain. Some of these agents, for example, methylphenidate are synthesized by methods that are rather distinct from those used for the synthesis of most of the other phenalkylamines (Panizzon, 1944). However, certain other agents, such as phenmetrazine, phendimetrazine, and aminorex, can be synthesized using some of the already described methods. Phenmetrazine can be prepared from norephedrine by acylation, reduction, and cyclization as shown in Scheme 6a (Clarke, 1965). Phendimetrazine, the N-methyl analogue of phenmetrazine, has been prepared via a similar hydroxyethyl intermediate obtained by reaction of ephedrine with ethylene oxide. Reaction of phenylethanolamine with cyanogen bromide results in spontaneous cyclization of the hydroxycyanamide to aminorex (Scheme 6b) (Poos *et al.*, 1963). Use of norephedrine in this synthesis in place of the phenylethanolamine provides *cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (i.e., 4-methylaminorex)

Scheme 5

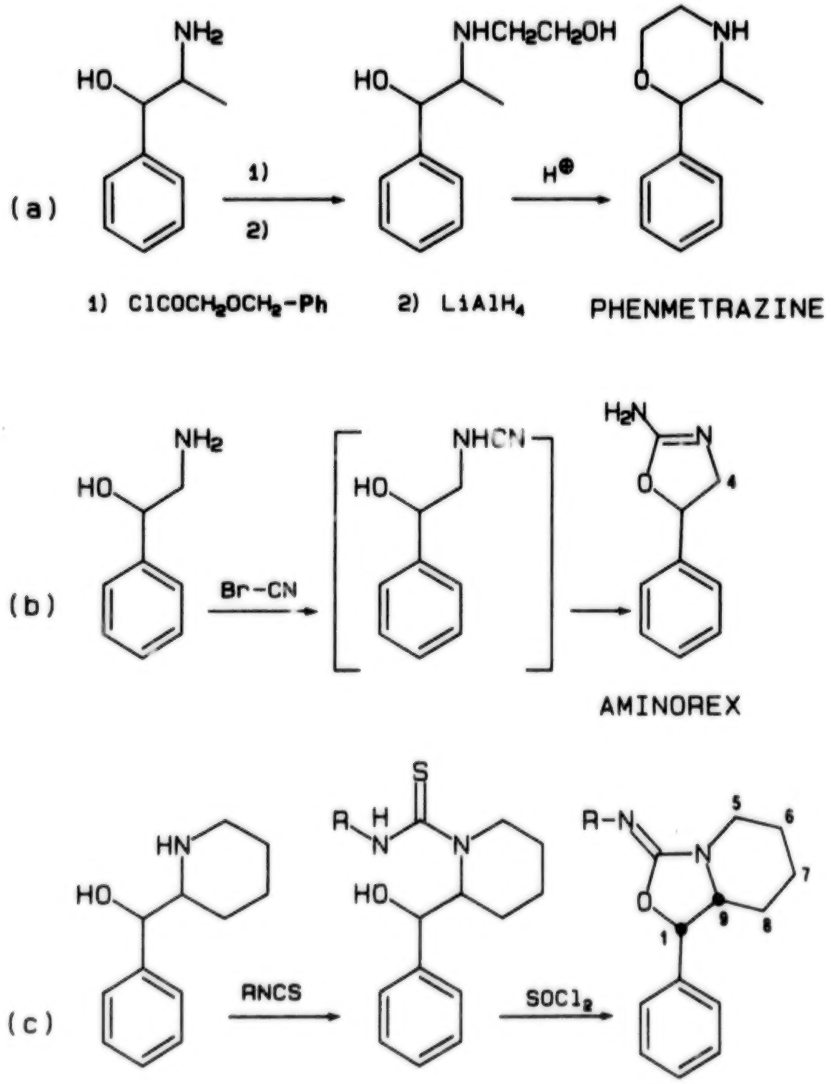
Synthesis of N-substituted phenalkylamines.



(Poos *et al.*, 1963). This latter agent is an abused substance that has appeared on the street as U4Euh (Inaba and Brewer, 1987). A series of perhydro oxazolo[3,4-a]pyridines (i.e., cyclic aminorex analogues) has also been prepared and evaluated (Scheme 6c) (Wollweber *et al.*, 1978, 1980; Pohl and Wollweber, 1978). Because these molecules possess two asymmetric centers (i.e., the 1- and 9-positions), four diastereoisomers are possible; Wollweber and co-workers (1980) have examined the activity of a number of unsubstituted and aryl-substituted derivatives including their isomers.

Scheme 6

Synthesis of some cyclic phenalkylamine analogues.



Stimulus Properties of Amphetamine Analogues

Psychoactive phenalkylamines can be divided into several pharmacological categories of which the two largest are (a) the central stimulants (i.e., amphetamine-like agents) and (b) the hallucinogens (i.e., DOM-like agents) (Glennon, 1987). We have been studying the mechanisms of action and structure-activity relationships of psychoactive agents for several years now. However, as a prelude to such studies involving phenalkylamines, it was necessary to determine which phenalkylamines are amphetamine-like and which are DOM-like. To this extent, we have used a drug discrimination paradigm, with rats as subjects, to evaluate a large number of such agents. Briefly, the drug discrimination paradigm is a "detection" procedure whereby animals can be trained to recognize the stimulus effects produced by a given dose of training drug. Once trained, these animals can be administered doses of novel agents ("challenge drugs") in order to determine if these agents produce stimulus effects similar to those of the training drug. This process is known as "stimulus generalization". Because stimulus generalization is a dose-related phenomenon, the data obtained are quantitative as well as qualitative. In effect, the animals can indicate (a) whether a challenge drug produces stimulus effects similar to those of a particular training drug and, if it does, (b) how potent it is relative to the training drug. Thus, using animals trained to discriminate either 1.0 mg/kg of (+)amphetamine sulfate or 1.0 mg/kg of racemic DOM hydrochloride from vehicle, we have examined a number of phenalkylamine derivatives. See reviews by Glennon (1987) and by Young and Glennon (1986) for detailed discussions of the procedure and the results of studies on various phenalkylamine derivatives.

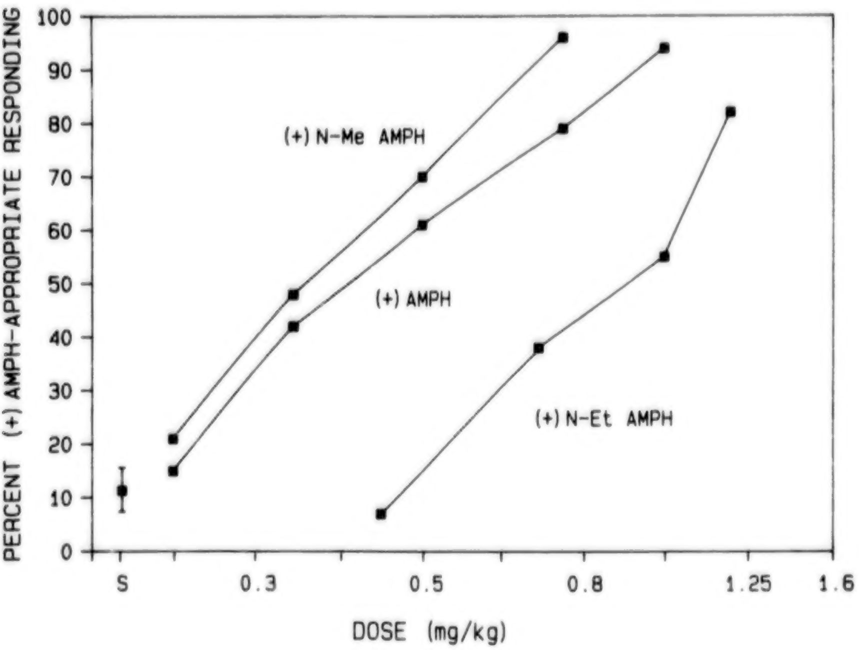
Studies with (+) AMPH and DOM-trained animals

Presented in Tables 1–3 are some representative data generated in our laboratory from animals trained to discriminate either (+)amphetamine or DOM from saline; although some of the data are new, most of it has been previously published. The potencies of amphetamine, its N-methyl, N-ethyl, N-hydroxy, monomethoxy, benzylic carbonyl, and several other derivatives, in producing amphetamine-like stimulus effects are shown in Table 1. [A typical dose-response curve using (+)amphetamine-trained animals is shown as Figure 1.] None of these agents (with the exception of racemic MDA) produced DOM-like effects in the DOM-trained animals. [MDA is the only agent that produces both amphetamine-like and DOM-like stimulus effects (with the S-isomer being primarily responsible for the amphetamine-like effects and the R-isomer for DOM-like effects).] Data for DOM-like activity are shown in Table 3; none of the agents (with the exception of MDA) that produced DOM-like effects produced amphetamine-like effects in (+)amphetamine-trained animals.

From the data provided in Tables 1 and 3, it is possible to develop structure-activity relationships (SARs). A discussion of the SARs is beyond the scope of this review; nevertheless, even a casual inspection of these tables will reveal that the SAR for amphetamine-like stimulus effects is distinctly different from that for DOM-like stimulus effects.

It should be emphasized that lack of stimulus generalization between two agents does not necessarily imply that the agents can not share some behavioral components. That is, an agent may behave primarily as a hal-

Figure 1

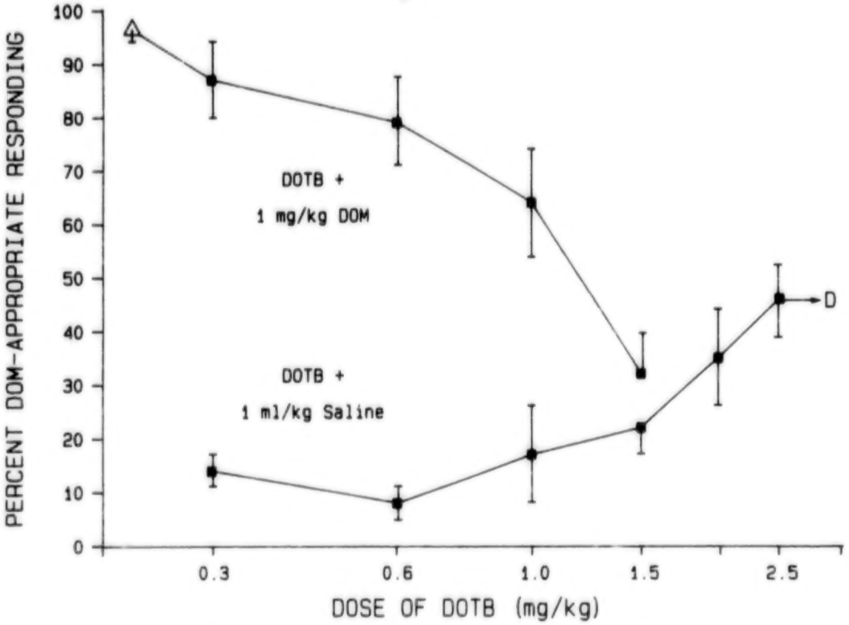


Drug discrimination results using rats trained to discriminate (+)amphetamine sulfate from saline. Also shown are the results of substitution tests (i.e., tests of stimulus generalization) using (+)N-monomethylamphetamine and (+)N-monoethylamphetamine. (Percent drug-appropriate responding is the percent of total responses made on the drug-designated lever.)

lucinogen in humans but, at the same time, produce a minor central stimulant effect. Thus, it is possible that stimulus generalization will occur in the DOM-trained animals but not in the amphetamine-trained animals. On the other hand, certain anorectic agents produce amphetamine-like central stimulation in humans; although many of these agents remain to be investigated in drug discrimination studies, Dr. R. Young in our laboratory has shown that aminorex, for example, is at least as potent as amphetamine (Young, 1987). The amphetamine-stimulus also generalizes to other anorexics such as phenmetrazine and phendimetrazine (Young, 1987).

Certain phenalkylamine derivatives appear to produce neither amphetamine-like (Table 2) nor DOM-like (see footnote to Table 3) stimulus effects. Because an agent produces neither amphetamine-like nor DOM-like stimulus effects, it should not be assumed that the agent is behaviorally inactive. It does suggest (a) that the stimulus effects produced by the agent are sufficiently dissimilar to those produced by either amphetamine or DOM so as to be non-recognizable by these animals, (b) that the agent can produce some other effect (at low doses) that interferes with an am-

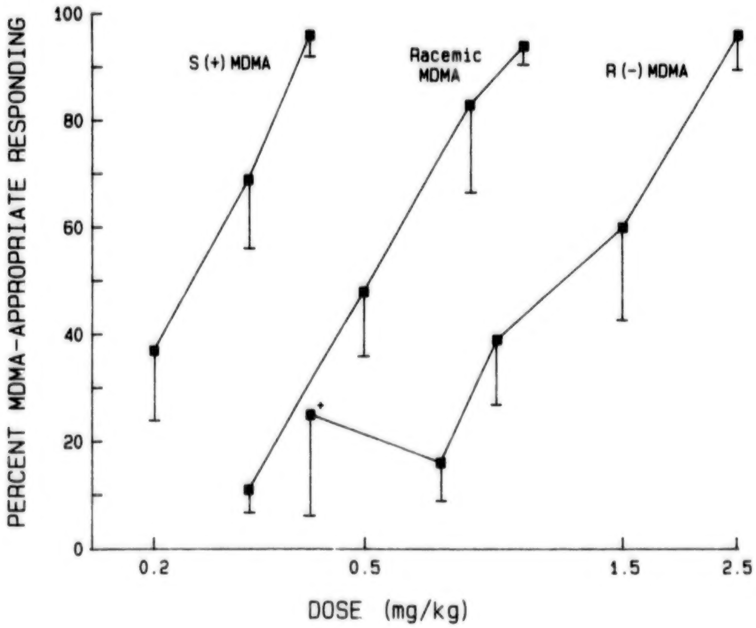
Figure 2



Antagonism of the DOM-stimulus by DOTB. Upper curve is the effect of doses of DOTB administered 1 min prior to 1.0 mg/kg of DOM (15-min presession injection interval) in DOM-trained rates. Lower curve is the control curve (DOTB administered 1 min prior to 1.0 ml/kg of saline using the same animals). Doses of >2.5 mg/kg of DOTB (in combination with saline) resulted in distruption of behavior, D). Open triangle represents the effect of 1.0 mg/kg of DOM (in the absence of DOTB).

phetamine-like or DOM-like effect (that might otherwise be recognized at higher doses) and essentially masks the amphetamine-like or DOM-like effect, (c) that the agent may be an antagonist, or (d) that the agent may, indeed, be inactive (intrinsically inactive or unable to penetrate the blood-brain barrier). For example, the 4-hydroxy analogue of amphetamine (i.e. 4-OH AMPH), a pharmacologically active agent with peripheral actions, apparently does not readily cross the blood-brain barrier; the amphetamine-stimulus does not generalize to 4-OH AMPH and in fact 4-OH AMPH fails to serve as a training drug in animals (see Young and Glennon (1986) for further discussion). Another example is DOTB, the 4-*tert*-butyl analogue of 2,5-DMA; the DOM-stimulus does not completely generalize to DOTB (i.e., DOTB elicits $< 80\%$ DOM-appropriate responding), however, administration of low doses of DOTB in combination with the training dose of DOM results in partial antagonism of the DOM stimulus (Fig 2). (The antagonism is not complete; administration of higher doses of DOTB results in partial generalization.) Thus, the most useful and reliable data are those obtained in cases where stimulus generalization (i.e., $> 80\%$ training-drug-appropriate responding) occurs;

Figure 3



Dose response curve for racemic MDMA in rats trained to discriminate 1.0 mg/kg of MDMA from saline. Also shown are the results of substitution tests (i.e., tests of stimulus generalization) using the optical isomers of MDMA.

when stimulus generalization does not occur, additional studies are necessary to further characterize the agent.

Studies with MDA- and MDMA-trained animals

As mentioned above, stimulus generalization occurred with MDA in animals trained to discriminate (+)amphetamine (Glennon *et al.,* 1982; Kamien *et al.,* 1986; Evans and Johanson, 1986) and DOM (Table 3) from saline, suggesting that MDA is capable of producing both amphetamine-like and DOM-like stimulus effects. As a consequence, we trained rats to discriminate 1.5 mg/kg of MDA from saline. Consistent with our earlier findings, the MDA-stimulus generalized to (+)amphetamine and DOM. The MDA-stimulus also generalized to 3,4-DMA, 2,3-MDA, MDMA, cocaine and LSD (Young and Glennon, 1986).

In a separate study, we trained a small group of rats to discriminate 1.0 mg/kg of racemic MDMA from saline (Glennon *et al.,* 1986b). Stimulus generalization occurred with both optical isomers of MDMA (ED50=0.23 and 1.0 mg/kg for S(+)- and R(−)MDMA, respectively) (Glennon *et al.,* 1986b, 1987) to provide an enantiomeric potency ratio (R/S) of 4. Recently, using rats trained to discriminate 1.5 mg/kg of MDMA from saline, Schechter (1987) has reported a potency ratio of 2.

However, Schechter (1987) has also found that racemic MDMA is more potent than either of its isomers whereas we have found that racemic MDMA (ED50=0.52 mg/kg) is more potent than R(−)MDMA but less potent than S(+)MDMA (see Figure 3) (Glennon *et al.,* 1986b). In a series of preliminary studies, we have also found that N-OH MDA results in stimulus generalization in the MDMA-trained animals. Because neither the amphetamine-stimulus nor the DOM-stimulus generalized to N-OH MDA (see Tables 2 and 3), the use of MDMA as a training drug may provide some interesting answers to questions regarding related agents such as 2,3-MDA, 3,4-DMA, and MDE (3,4-methylenedioxyethylamphetamine.

Summary

With regard to the synthesis of phenalkylamines, the two most popular methods are the phenylpropanone method and the Knoevenagel reaction. Both are fairly general reactions but the former is somewhat limited due to the lack of commercial availability of precursor phenylpropanones. A wide variety of phenylpropanones is available from a modification of the Knoevenagel reaction but synthesis of the propanones in this manner is infrequently reported in the literature. However, this route may be attractive to clandestine laboratories because it avoids the use of metal hydride reducing agents (that are normally required in the final step of the Knoevenagel reaction).

In addition to the above two reactions (and their modifications), other synthetic routes for the preparation of phenalkylamines have been reported in the literature; some of these were reviewed (Schemes 2–4). One of the key conclusions of this review is that there is a diversity of synthetic routes and a variety of different starting materials that can be employed in the preparation of these phenalkylamines.

In the last half of this review, the use of the drug discrimination method was discussed. This operant method appears to be of value in the classification of phenalkylamines as being either amphetamine-like or DOM-like. Because the method provides quantitative as well as qualitative results, it is possible to obtain data on the relative potencies of the agents being investigated. The method is also sensitive to the stereoselective effects of drugs and, as such, is suitable for the examination of optical isomers. Though not specifically discussed herein, the method is also useful for (a) investigating the activity of metabolites, (b) studying mechanisms of action, (c) examining potential antagonists, and (d) generating structure-activity relationships.

Many phenalkylamines (including certain of their precursors) are contolled substances. However, certain phenalkylamines are not controlled and, given the wide variety of starting materials, it would certainly be difficult to limit/monitor the sale of all possible precursors. One large group of phenalkylamines that (for the most part) are not controlled are the N-substituted phenalkylamines. N-Alkyl derivatives of hallucinogenic phenalkylamines are generally less potent than their primary amine counterparts; nevertheless, such agents are still active. N-Alkyl derivatives of amphetamine-like phenalkylamines are also active and the simpler derivatives (such as the N-monomethyl analogues) are about as potent as their parent primary amines. A final category of N-substituted agents that should not be ignored are the N-OH derivatives. Very little information is available on these types of agents; however, the N-OH analogue of amphetamine, for example, appears to produce amphetamine-like effects.

Many of the known phenalkylamine analogues have not been thoroughly investigated. Given the number and diversity of synthetic routes available for the preparation of phenalkylamines, and because the SARs of these agents are at least fairly well understood, many more remain to be designed and synthesized. In order to gather information on the potential abuse liability of these agents, it is important to continue to explore relevant pharmacological procedures and to further develop the SARs of the available agents.

References

Aldous, F. A. B., Barrass, B. C., Brewster, K., Buxton, D. A., Green, D. M., Pinder, R. M., Rich, P., Skeels, M. and Tutt, K. J. Structure-activity relationships in psychotomimetic phenalkylamines. *J. Med. Chem.* 17: 1100–1111, 1974.

Allen, A. C. and Kiser, W. O., Methamphetamine from ephedrine: 1. chloroephedines and aziridines, *J. Forensic Sci.,* 32(4): 953–962, 1987.

Bailey, K., By, A. W., Legault, D. and Verner, D. Identification of the N-methylated analogs of hallucinogenic amphetamines and some isomers. *J. Assoc. Off. Analyt. Chem.* 58: 62–69, 1975.

Barfknecht, C. F. and Nichols, D. E. Potential psychotomimetics. Bromomethoxyamphetamines. *J. Med. Chem. 14: 370–372, 1971.*

Beckett, A. H., Kirk, G., and Sharpen, A. J. The configuration of alpha-methyldopamine. *Tetrahedron* 21: 1489–1493, 1965.

Benington, F. and Morin, R. D. Synthesis of 2,3,6-trimethoxy-β-phenethylamine. *J. Med. Chem.* 14: 375–376, 1971.

Benington, F., Morin, R. D. and Clark, L. C. Behavioral and neuropharmacological actions of N-aralkylhydroxylamines and their O-methyl ethers. *J. Med. Chem.* 8: 100–104, 1965.

Braun, U., Shulgin, A. T. and Braun, G. Centrally active N-substituted analogs of 3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxyamphetamine). *J. Pharm. Sci.* 69: 192–195, 1980a.

Braun, U., Shulgin, A. T. and Braun, G. Prufung auf zentrale aktivitat und analgesie von N-substituierten analogen des amphetamin-derivates 3,4-methylenedioxyphenylisopropylamin. *Drug Res.* 30: 825–830, 1980b.

Clark, C. C. The identification of methoxy-N-methylamphetamines. *J. Forensic Sci.* 29: 1056–1070, 1984.

Coutts, R. T. and Malicky, J. L. The synthesis of four possible in vitro metabolites of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). *Can. J. Chem.* 52: 395–399, 1974.

Evans, S. M. and Johanson, C. E. Discriminative stimulus properties of 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine in pigeons. *Drug Alcohol Depend.* 18: 159–164, 1986.

Fujisawa, T., Okada, M. and Deguchi, Y. 1-(β-Diethylaminoethoxyphenyl)-3-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline. Japan. Patent 8573 1956; *Chem. Abstr.* 52: 11965, 1958.

Gal, J., Gruenke, L. D. and Castagnoli, N. N-Hydroxylation of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane by rabbit liver microsomes. *J. Med. Chem.* 18: 683–688, 1975.

Gilsdorf, R. T. and Nord, F. F. Reverse addition of lithium aluminum hydride to nitroolefins. *J. Am. Chem. Soc.* 74: 1837–1842, 1952.

Glennon, R. A. Hallucinogenic Phenylisopropylamines: Stereochemical Aspects. In: Handbook of Stereoisomers: Drugs in Psychopharmacology, D. F. Smith, ed., Boca Raton, CRC Press, 1984. pp 327–368.

Glennon, R. A. Psychoactive Phenylisopropylamines. In: Psychopharmacology: The Third Generation of Progress, H. Y. Meltzer, ed., New York, Raven Press, 1987. pp 1627–1634.

Glennon, R. A., Young, R., Rosecrans, J. A. and Anderson, G. M. Discriminative stimulus effects of MDA analogs. *Biol. Psychiat.* 17: 807–814, 1982.

Glennon, R. A., McKenney, J. D., Lyon, R. A. and Titeler, M. 5-HT1 and 5-HT2 binding characteristics of 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane analogs. *J. Med. Chem.* 29: 194–199, 1986a.

Glennon, R. A., Titeler, M., Lyon, R. A. and Yousif, M. Y. MDMA ("Ecstasy"): Drug discrimination and brain binding properties. *Soc. Neurosci. Abstr.* 12: 919, 1986b.

Glennon, R. A., Little, P. J., Rosecrans, J. A. and Yousif, M. Y. The effect of MDMA (Ecstasy) and its optical isomers on schedule-controlled responding in mice. *Pharmacol. Biochem. Behav.* 26: 425–426, 1987a.

Glennon, R. A., Yousif, M., Naiman, N. and Kalix, P. Methcathinone: A new and potent amphetamine-like agent. *Pharmacol. Biochem. Behav.* 26: 547–551, 1987b.

Gorrod, J. W. and Jenner, P. Metabolic N-oxidation products of aliphatic amines as potential mediators in amine pharmacology. *Int. J. Clin. Pharmacol. Biopharm.* 12: 180–185, 1975.

Hartung, W. H., Munch, J. C., Miller, E. and Crossley, F. Aminoalcohols. VII. Phenolic arylpropanolamines. *J. Am. Chem. Soc.* 53: 4149–4160, 1931.

Ho, B. T., McIsaac, W. M., An, R., Tansey, L. W., Walker, K. E., Englert, L. F. and Noel, M. B. Analogs of α-methylphenethylamines

(Amphetamine). I. Synthesis and pharmacological activity of some methoxy and/or methyl analogs. *J. Med. Chem.* 13: 26–30, 1970.

Inaba, D. and Brewer, L. M. U4Euh. Personal communication, 1987.

Jacob, P., Anderson, G., Meshul, C. K., Shulgin, A. T. and Castagnoli, N. Monomethylthio analogues of 1-(2,4,5-trimethoxyphenyl)-2-aminopropane. *J. Med. Chem.* 20: 1235–1239, 1977.

Kamien, J. B., Johanson, C. E., Schuster, C. R. and Woolverton, W. L. The effects of (±)methylenedioxymethamphetamine and (±)methylenedioxyamphetamine in monkeys trained to discriminate (+)amphetamine from saline. *Drug Alcohol Depend.* 18: 139–147, 1986.

Kiefer, E. F. A rapid and convenient preparative procedure for phenethylamines. *J. Med. Chem.* 15: 214, 1972.

Major, R. T. and Ohly, K. W. Derivatives of hydroxylamine: Central nervous system stimulants. *J. Med. Chem.* 4: 51–65, 1961.

Mourad, M. S., Varma, R. S. and Kabalka, G. W. A convenient reduction of α,β-unsaturated nitroalkenes to alkylamines using boron hydrides. *Synth. Commun.* 14: 1099–1104, 1984.

Nichols, D. E., Barfknecht, C. F., Rusterholz, D. B., Benington, F. and Morin, R. D. Asymmetric synthesis of enantiomers of psychotomimetic amphetamines. *J. Med. Chem.* 16: 480–483, 1973.

Nichols, D. E. and Kostuba, L.J. Steric effects of substituents on phenethylamine hallucinogens. 3,4-Methylenedioxyamphetamine analogs on the dioxole ring. *J. Med. Chem.* 22: 1264–1267, 1979.

Panizzon, L. La preparazione di piridil- e piperidil-acetonitrili e di alcuni prodotti di trasformazione. *Helv. Chim. Acta* 27: 1748–1756, 1944.

Patrick, T. M., McBee, E. T. and Hass, H. B. Synthesis of arylpropylamines. I. From allyl chloride. *J. Am. Chem. Soc.* 68: 1009–1011, 1946.

Pohl, H. U. and Wollweber, H. Stereochemische untersuchungen uber arzneimittel. 6. Mitt. Chiroptische eigenschaften von phenyl-2-piperidylcarb-inolen und deren cyclisierungsprodukten. *Eur. J. Med. Chem.* 13: 127–139, 1978.

Rabusic, E. and Gregor, M. Aminoalkylation of phenol ethers. Spisy Privodoved. Fak. Univ. Brne 480: 85–92, 1967; *Chem Abstr.* 68: 86944, 1968.

Sayish, A. A. R., Ulrich, H. and Green, M. Synthesis of 2,5-dimethoxy-3-methylbenzaldehyde and 2,5-dimethoxy-4-methylbenzaldehyde. *J. Chem. Soc.* 3482–3484, 1964.

Schaeffer, J. C., Cho, A. K., Nagami, G. T. and Takimoto, G. S. Inhibition of synaptosomal accumulation of 1-norepinephrine I: N-Arylalkyl and N-aryloxyalkyl dl-amphetamines and related compounds. *J. Pharm. Sci.* 64: 1462–1469, 1975.

Schechter, M.D. MDMA as a discriminate stimulus: Isomeric comparisons. *Pharmacol. Biochem. Behav.* 27: 41–44, 1987.

Schrecher, A. W. and Hartwell, J. L. The absolute configuration of lignans. *J. Am. Chem. Soc.* 79: 3827–3833, 1957.

Sepulveda, S., Valenzuela, R. and Cassels, B. K. Potential psychotomimetics. New bromoalkoxyamphetamines. *J. Med. Chem.* 15: 413–415, 1972.

Shulgin, A. T. The six trimethoxyphenylisopropylamines (trimethoxyamphetamines). *J. Med. Chem.* 9: 445–446, 1966.

Shulgin, A. T. The background and chemistry of MDMA. *J. Psychoact. Drugs* 18: 291–304, 1986.

Shulgin, A. T. and Carter, M. F. Centrally active phenethylamines. *Psychopharm. Commun.* 1: 93–98, 1975.

Sinnema, A. and Verweij, A. M. A. Impurities in illicit amphetamine: A review. *Bull. Narc.* 33: 37–54, 1981.

Standridge, R. T., Howell, H. G., Gylys, J. A., Partyka, R. A. and Shulgin, A. T. Phenalkylamines with potential psychotherapeutic activity. 2-Amino-1-(2,5-dimethoxy-4-methyl)butane. *J. Med. Chem.* 19: 1400–1404, 1976.

Stone, C. A. Hypotensive 4,5-dihydroxy-α-methylphenethylamine derivatives. Belg. Patent 633,963 1963; *Chem. Abstr.* 61: 6953 1964.

Wollweber, H., Pohl, H. U. and Stoepel, K. Stereochemische untersuchungen uber arzneimittel. 7. Mitt. 1-Phenyl-3-imino-perhydro-3H-thiazolo[3,4-a]pyridine, stereochemie und blutdrucksteigernde wirksamkeit. *Eur. J. Med. Chem* 13: 141–148, 1978.

Wollweber, H., Hiltmann, R., Stoepel, K. and Kroneberg, H. G. Stereochemische untersuchungen uber arzneimittel. 8. Mitt. 1-Phenyl-3-imino-perhydro-3H-oxazolo[3,4-a]pyridine, mit blutdrucksteigernder wirksamkeit. *Eur. J. Med. Chem.* 15: 111–117, 1980

Young, R. Unpublished data; personal communication, 1987.

Young, R. and Glennon, R. A. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. *Med. Res. Rev.* 6: 99–130, 1986.

Zwieg, J. S. and Castagnoli, N. In vitro O-demethylation of the psychotomimetic amine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane. *J. Med. Chem.* 20: 414–421, 1977.

BLANK PAGE

4-Phenylpiperidine Analgesics, Fentanyl and Fentanyl Analogues Methods of Synthesis

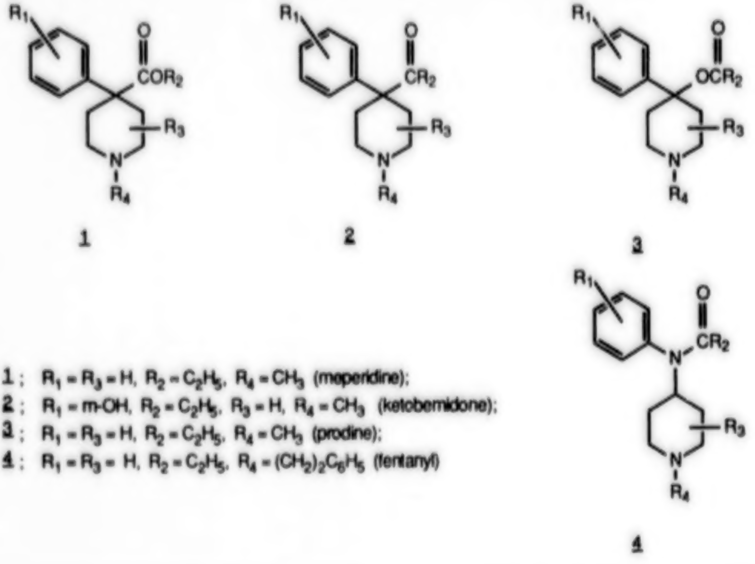
F. Ivy Carroll, Ph.D. and George A. Brine, Ph.D.

Introduction

There are thousands of synthetic piperidine derivatives which show analgesic activity equal to or greater than morphine in animals. Many of these compounds have been evaluated in humans, and several are used clinically. Compared to morphine, the substituted piperidines are structurally simpler and possess much more conformational freedom. Since the synthesis of substituted piperidines is relatively easy and since these compounds possess increased conformational flexibility, many hypotheses concerning structural requirements for analgesic activity have been developed. From a practical point of view these studies have led to the four classes of analgesics listed in Figure 1: (a) the meperidine family, *1*; (b) the ketobemidone family, *2*; (c) the prodine family, *3*; and (d) the fentanyl family, *4*.

Figure 1

Substituted Piperidine Classes of Analgesics



1; $R_1 = R_3 = H$, $R_2 = C_2H_5$, $R_4 = CH_3$ (meperidine);
2; $R_1 = m\text{-}OH$, $R_2 = C_2H_5$, $R_3 = H$, $R_4 = CH_3$ (ketobemidone);
3; $R_1 = R_3 = H$, $R_2 = C_2H_5$, $R_4 = CH_3$ (prodine);
4; $R_1 = R_3 = H$, $R_2 = C_2H_5$, $R_4 = (CH_2)_2C_6H_5$ (fentanyl)

In this chapter an overview of the synthetic routes to these four classes of analgesics is provided. The emphasis has been placed on synthetic methods which are reasonably well-known, relatively easy to conduct, and that have been applied to the synthesis of either clinically useful compounds or close analogues and/or compounds that are known to have been produced in clandestine laboratories. Much of the information reported is taken from previous reviews (Casy and Parfitt, 1986; Jacobson *et al.*, 1971; Johnson and Milne, 1981; Lenz *et al.*, 1986) and some original reports. In the prodine and fentanyl classes the synthetic routes are illustrated by selected examples from the authors' laboratory. Much of our work on these classes has been carried out under the auspices of the United States National Institute on Drug Abuse (NIDA) and the United States Drug Enforcement Administration (DEA).

Synthesis of Meperidine, Ketobemidone and Prodine Analgesics

Structurally the meperidine, ketobemidone and prodine classes are 4-carbalkoxy-, 4-ketoxy- and 4-acyloxy-4-arylpiperidines, respectively. In contrast, the fentanyl family which is the most potent of the four classes has the 4-anilinopiperidine structure. Synthetic procedures used to prepare key compounds in each of the first three classes are presented in this section. Because of their structural difference and personal experience with the fentanyl analgesics, synthetic routes to this class are discussed in a subsequent section.

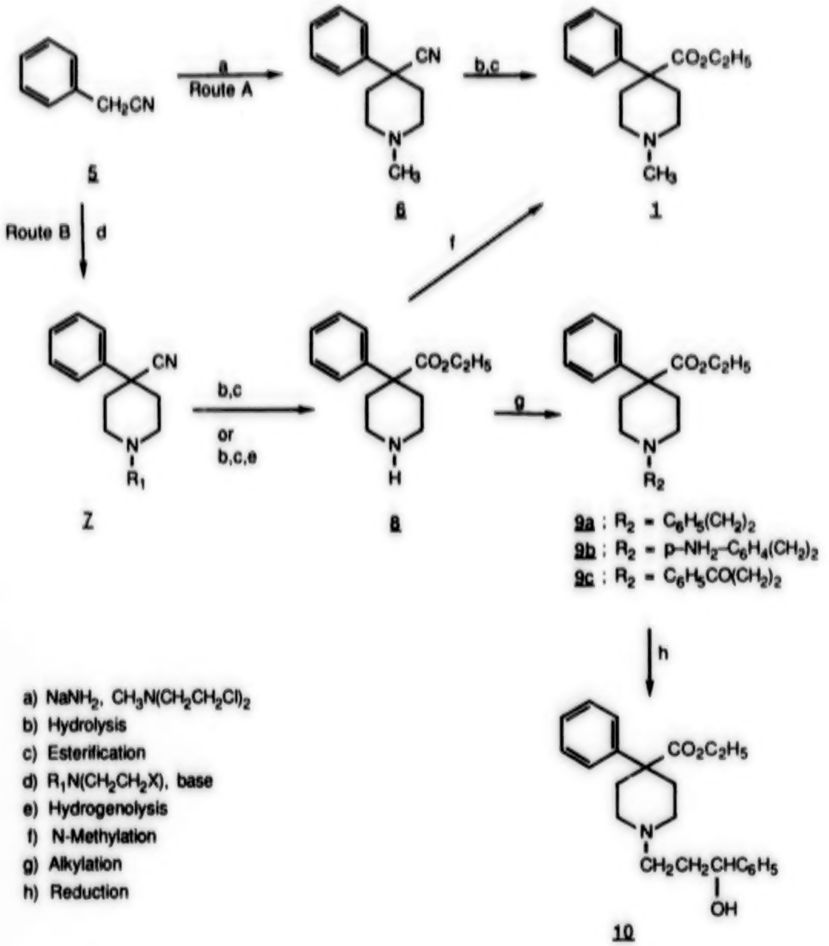
a) Meperidine

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (*1*. meperidine) was introduced by Eisleb and Schaumann in 1939 and remains a popular analgesic. In addition to meperidine, several N-substituted normeperidine analogues have shown clinical utility.

The original synthetic procedure that Eisleb used to prepare meperidines is shown in Scheme 1 (Route A). Condensation of the key starting material, phenylacetonitrile (*5*), with bis(2-chloroethyl)methylamine gives the 4-cyano-4-phenylpiperidine (*6*). Subsequent acid hydrolysis of *6* followed by esterification yields meperidine (*1*). Later modifications involved the use of less toxic nitrogen mustards in the first step (Route B). The resultant intermediate *7* with R_1 equal to a benzyl, arylsulfonyl or carbalkoxy substituent is converted to N-normeperidine (*8*) by hydrogenolysis or hydrolysis. N-Methylation of *8* gives meperidine (*1*). In addition, conversion of *8* to N-substituted normeperidine analogues is accomplished using appropriately activated groups and standard methods for amine alkylation.

Meperidine has also been prepared by alternate routes in which the piperidine ring is closed by reaction of methylamine with a 1,5-dichloro compound prepared in two steps from phenylacetonitrile (*5*) (cf. Scheme

Scheme 1

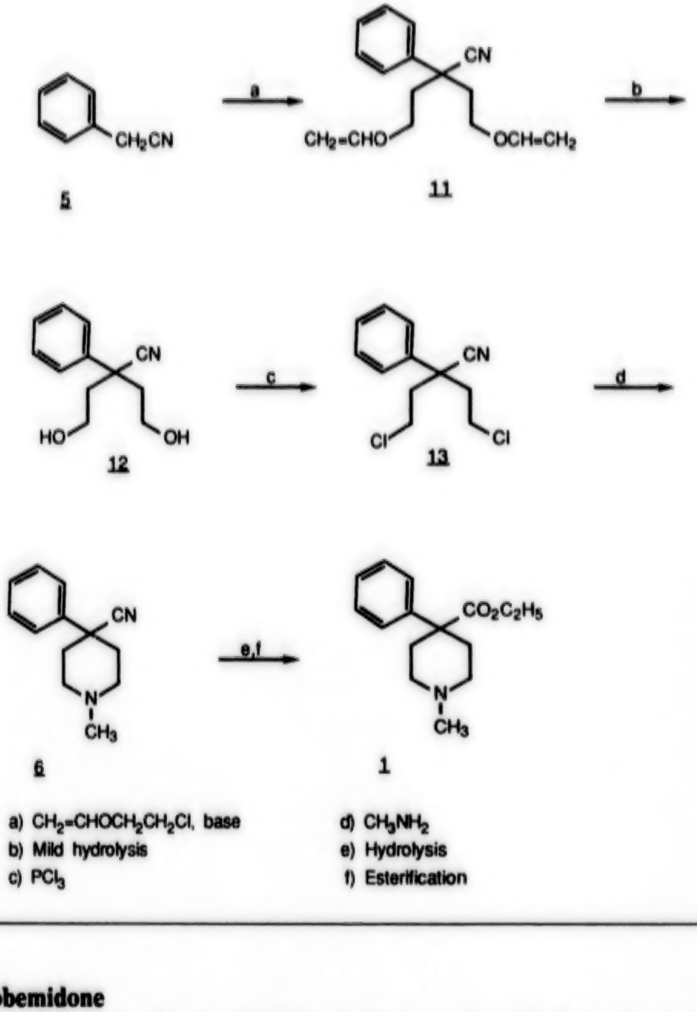


a) $NaNH_2$, $CH_3N(CH_2CH_2Cl)_2$
b) Hydrolysis
c) Esterification
d) $R_1N(CH_2CH_2X)$, base
e) Hydrogenolysis
f) N-Methylation
g) Alkylation
h) Reduction

2). In this procedure *5* is first dialkylated with two equivalents of 2-chloroethyl vinyl ether to give the bis-adduct *11*. Milk hydrolysis of *11* gives the bis-hydroxyethyl compound (*12*). Conversion to the dihalide *13* followed by cyclization with methylamine gives *6* which is converted to meperidine as shown in Scheme 1.

However, the easiest and most practical synthesis of meperidine is that reported by Blicke *et al.* (1952) and shown in Scheme 3. Treatment of phenylacetonitrile (*5*) with 2-chloro-N,N-dimethylethylamine gives the bis-adduct *14*. When *14* as its mono or dihydrochloride salt is heated to its melting point, the 4-cyano-4-phenylpiperidine *6* is obtained. Subsequent conversion of meperidine is carried out as shown in Scheme 1.

Scheme 2



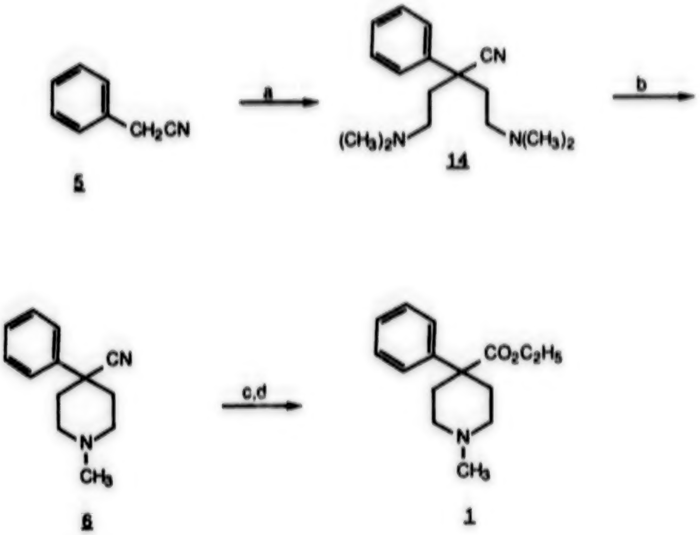
a) $CH_2{=}CHOCH_2CH_2Cl$, base
b) Mild hydrolysis
c) PCl_3
d) CH_3NH_2
e) Hydrolysis
f) Esterification

b) Ketobemidone

In addition to the meperidine analogues described in the previous section, a very large number of other analogues have been prepared. For the most part a substituent change at the piperidine C-4 position either abolishes or does not greatly improve analgesic activity. An exception is ketobemidone (*2*), which represents a twofold change from meperidine and which has analgesic activity equivalent to morphine. In the structure of ketobemidone (*2*), the phenyl becomes a m-hydroxyphenyl and the carboethoxy is changed to an ethylketo group.

Ketobemidone (*2*) can be prepared by the route shown in Scheme 4 (Avison and Morrison, 1950). Treatment of m-methoxyphenylacetonitrile (*15*) with bis(2-chloroethyl)methylamine under conditions similar to that described for the synthesis of *6* gives 4-cyano-4-(m-methoxyphenyl)-1-methylpiperidine (*16*). Subsequent treatment of *16* with ethylmagnesium

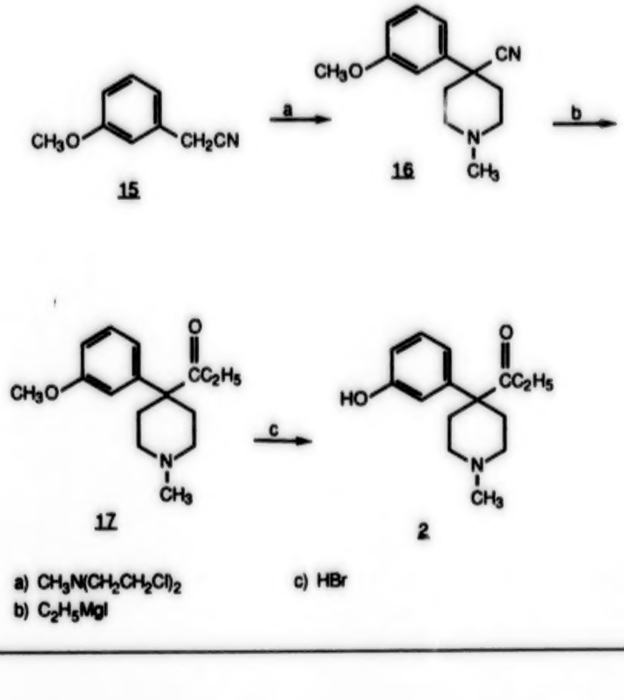
Scheme 3



a) $(CH_3)_2NCH_2CH_2Cl$, $NaNH_2$
b) Heat

c) Hydrolysis
d) Esterification

Scheme 4



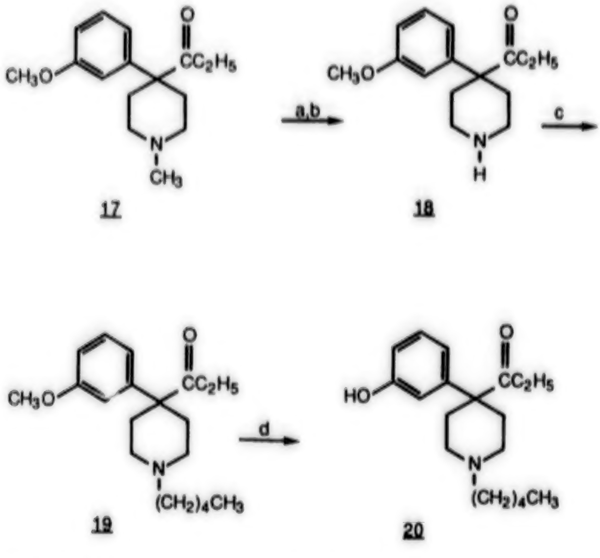
a) $CH_3N(CH_2CH_2Cl)_2$
b) C_2H_5MgI

c) HBr

iodide generates the C-4 ketone *17* which is O-demethylated with aqueous hydrobromic acid to give ketobemidone (*2*).

To our knowledge no ketobemidone analogues have been used clinically. However, 1-amyl-4-m-hydroxyphenyl-4-propionylpiperidine (*20*) is almost three times as potent as ketobemidone in mice. Its synthesis is shown in Scheme 5 (Oh-Ishi and May, 1973). The N-nor-2-ketobemidone (*18*) is obtained by treating *17* with ethyl chloroformate, followed by acid hydrolysis. Alkylation of *18* with amyl bromide gives the O-methyl protected compound *19*. O-Demethylation of *19* with hydrobromic acid provides *20*.

Scheme 5



a) C_2H_5OCOCl
b) Hydrolysis

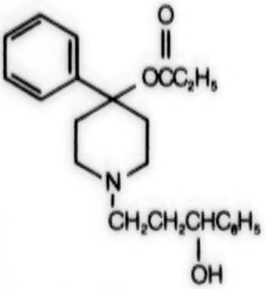
c) $CH_3(CH_2)_4Br$, K_2CO_3
d) HBr

c) Prodine

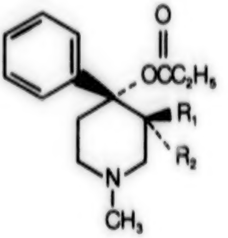
The replacement of the 4-carboethoxy group of meperidine by the 4-propionyloxy ($OCOC_2H_5$) group gives prodine (*3*), the so-called reversed ester of meperidine. The structure-activity correlations for prodine almost parallel those of the meperidine class of compounds. However, the prodine analogues generally show about a twenty-fold increase in activity relative to the meperidine analogues.

Similar to meperidine, replacement of the N-methyl by selected N-substituents increases analgesic activity and provides the most active compounds in this class. Maximum activity is found with the N-(3-phenyl-3-propanol) analogue (*21*) of prodine, which is 3200 times as active as meperidine. The introduction of an alkyl group in the piperidine 3-position of prodine gives a diastereoisomeric pair of cis and trans isomers. When the alkyl group is methyl, the trans isomer (*22*, α-prodine) is almost as potent as morphine, whereas the cis isomer (*23*, β-prodine) has at least three times the potency of morphine. α-Allylprodine (*24*) is ten times as active as β-allylprodine (*25*) and thirteen times as active as morphine in mice.

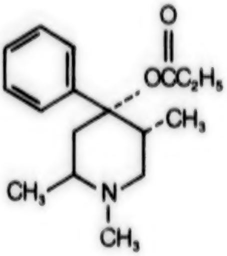
All possible dimethyl substituted piperidine analogues of prodine have been prepared and screened for analgesic activity. The most interesting analogue is the 2,5-dimethyl compound trimeperidine (*26*) which is used clinically in the USSR.



21



22 ; R_1 = H, R_2 = CH_3
23 ; R_1 = CH_3, R_2 = H
24 ; R_1 = C_3H_5, R_2 = H
25 ; R_1 = H, R_2 = C_3H_5



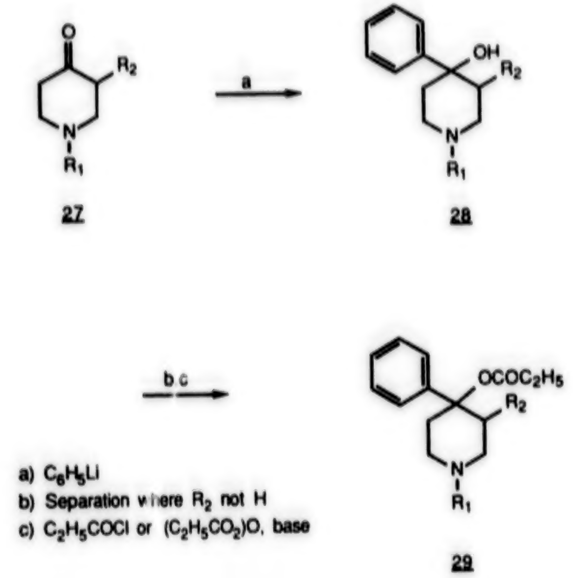
26

The general route used for the synthesis of prodine with and without a C-3 substituent is illustrated in Scheme 6. Addition of phenyllithium to the appropriate 4-piperidone (*27*) gives the 4-aryl-4-piperidinol intermediate (*28*). Acylation with propionyl chloride or anhydrides gives *29*. When R_2 is not hydrogen, the α- and β-isomers of the disastereoisomeric alcohols (*28*) are separated before acylation.

Prodine (*3*) and 1-(2-phenylethyl)-4-phenyl-4-acetoxypiperidine (*32*, PEPAP) were prepared using methods similar to those shown in Scheme 6. Treatment of the commercially available 4-piperidones (*30a*) and (*30b*) (cf. Scheme 7) with phenyllithium provided the alcohols (*31a*) and (*31b*), respectively. Esterification of alcohol (*31a*) with acetyl chloride and sodium carbonate in chloroform afforded 1-(2-phenylethyl)-4-phenyl-4-acetoxypiperidine (*32*). A similar esterification of alcohol (*31b*) with propionyl chloride gave 1-methyl-4-phenyl-4-propionoxypiperidine (*3*, prodine or MPPP). None of the toxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, *33*) was detected during the latter synthesis.

The 4-piperidones (*27*) (cf. Scheme 6) are the key starting materials for syntheses of the prodine family. In a few cases (cf. Scheme 7) these

Scheme 6



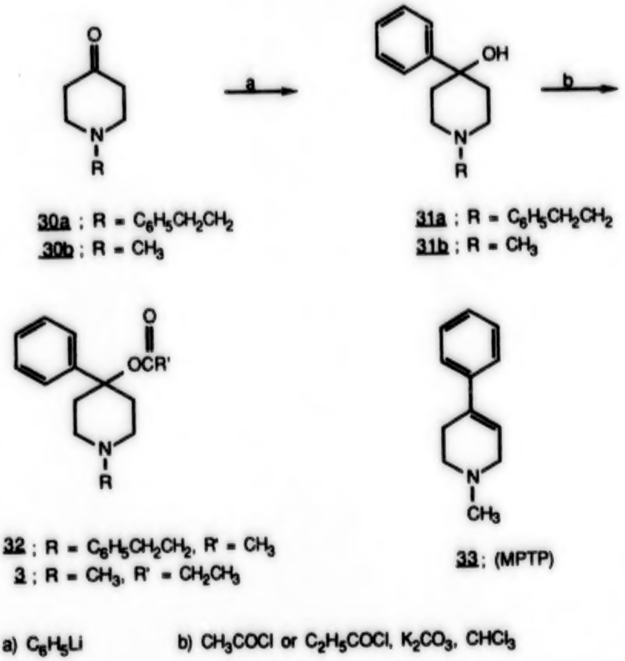
27

28

29

a) C_6H_5Li
b) Separation where R_2 not H
c) C_2H_5COCl or $(C_2H_5CO_2)O$, base

Scheme 7



30a ; R = $C_6H_5CH_2CH_2$
30b ; R = CH_3

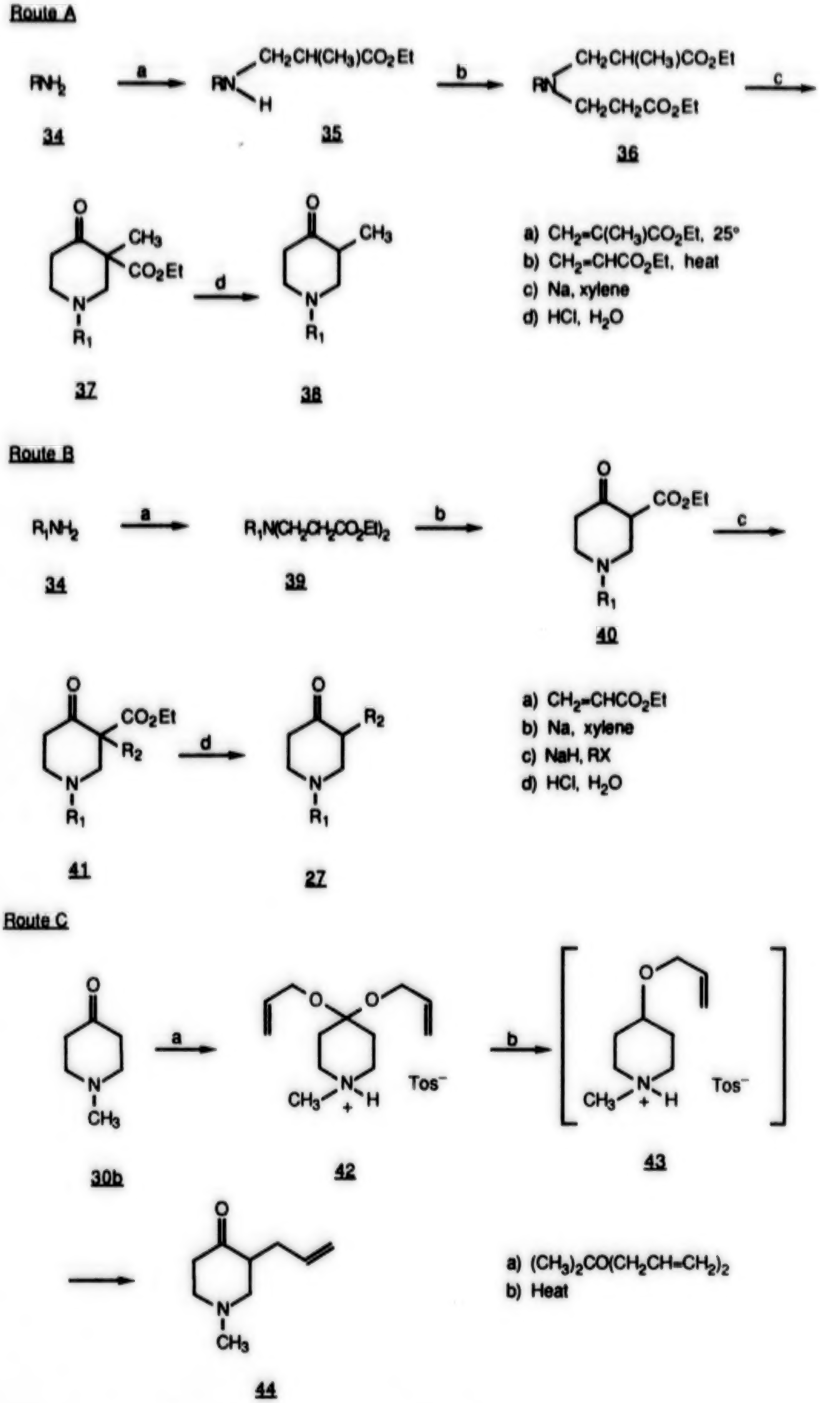
31a ; R = $C_6H_5CH_2CH_2$
31b ; R = CH_3

32 ; R = $C_6H_5CH_2CH_2$, R' = CH_3
3 ; R = CH_3, R' = CH_2CH_3

33 ; (MPTP)

a) C_6H_5Li b) CH_3COCl or C_2H_5COCl, K_2CO_3, $CHCl_3$

Scheme 8



Route A:

a) $CH_2{=}C(CH_3)CO_2Et$, 25°
b) $CH_2{=}CHCO_2Et$, heat
c) Na, xylene
d) HCl, H_2O

Route B:

a) $CH_2{=}CHCO_2Et$
b) Na, xylene
c) NaH, RX
d) HCl, H_2O

Route C:

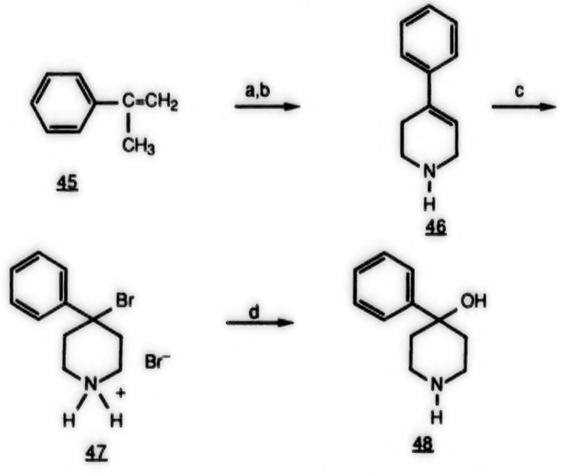
a) $(CH_3)_2CO(CH_2CH{=}CH_2)_2$
b) Heat

materials are commercially available. Three routes for the preparation of some substituted 4-piperidones are shown in Scheme 8. In route A is illustrated a general route for the synthesis of (±)-1-arylalkyl-3-methyl-4-piperidones (*38*) (Beckett *et al.*, 1959). The monoesters (*35*) are obtained by first reacting the amines (*34*) with ethyl methacrylate under mild conditions. Treatment of *35* with ethyl acrylate at higher temperature provides the diesters (*36*). Cyclization of the diesters (*36*) by Dieckmann procedures affords the cyclized products (*37*). Subsequent hydrolysis and decarboxylation gives *38*. Methyl methacrylate and methyl acrylate have been utilized in this sequence to prepare (±)-3-methyl-1-(β-phenethyl)-4-piperidone (*38*, $R = C_6H_5CH_2CH_2$) and (±)-1-benzyl-3-methyl-4-piperidone (*38*, $R = C_6H_5CH_2$). In the latter synthesis sodium methoxide was found to be preferable for the Dieckmann condensation.

An alternative synthesis of *38* and other C-3 substituted 4-piperidones (*27*) is shown in Route B. Treatment of the amines (*34*) with two moles of ethyl acrylate gives the diesters (*39*), which yield the cyclized products (*40*) on subjection to the Dieckmann condensation. Alkylation of *40* followed by dilute acid hydrolysis provides *27*. The first two steps of this sequence have been carried out using methyl acrylate and sodium methoxide (Jonczyk *et al.*, 1978; Zee *et al.*, 1981).

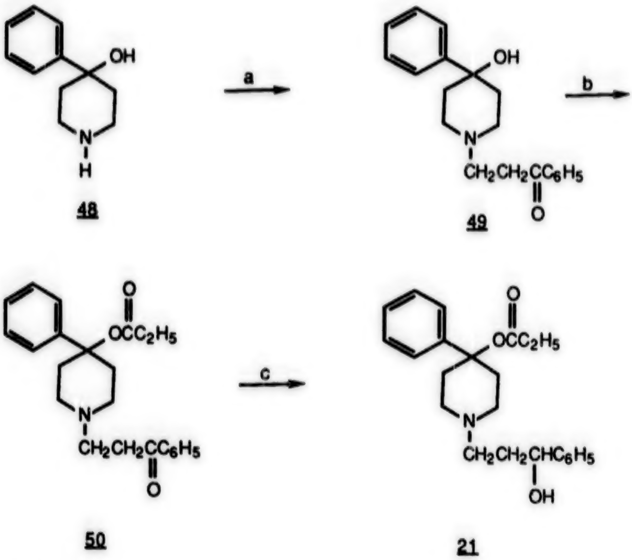
The synthesis of (±)-3-allyl-1-methyl-4-piperidone (*44*) (Bell and Portoghese, 1973) illustrates a third route to substituted 4-piperidones (Route C). Ketal exchange between acetone diallyl ketal and 1-methyl-4-piperidone (*30b*) in the presence of p-toluenesulfonic acid gives *42*. When intermediate (*42*) is heated, the elimination product (*43*) is obtained which is not isolated but allowed to undergo Claisen rearrangement to *44*.

Scheme 9



a) CH_2O, NH_4Cl b) HCl, H_2O c) HBr d) NaOH, H_2O

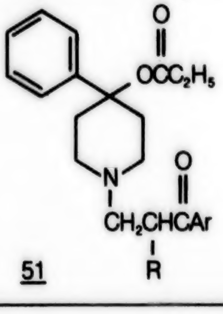
Scheme 10



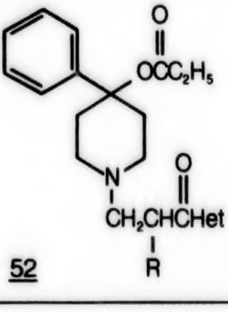
a) $C_6H_5COCH{=}CH_2$ b) C_2H_5COCl c) Reduction

N-Substituted-N-norprodine analogues can be prepared by choosing the appropriate N-substituted-4-piperidone (*27*). 4-Phenyl-4-piperidinol (*48*) prepared as shown in Scheme 9 (McElvain and Safranski, 1950; Schmidle and Mansfield, 1956) can serve as a key intermediate in the synthesis of N-substituted-N-norprodines. Condensation of α-methylstyrene (*45*) with formaldehyde and ammonium chloride followed by acid hydrolysis and basification gives the tetrahydropyridine *46*. Addition of hydrogen bromide to *46* provides *47* which on treatment with sodium hydroxide yields *48*. The synthesis of the highly potent analogue *21* from *48* is illustrated in Scheme 10.

A procedure similar to that shown in Scheme 10 has been used to prepare prodine analogues *51* and *52* where the R, Ar and Het groups were varied.



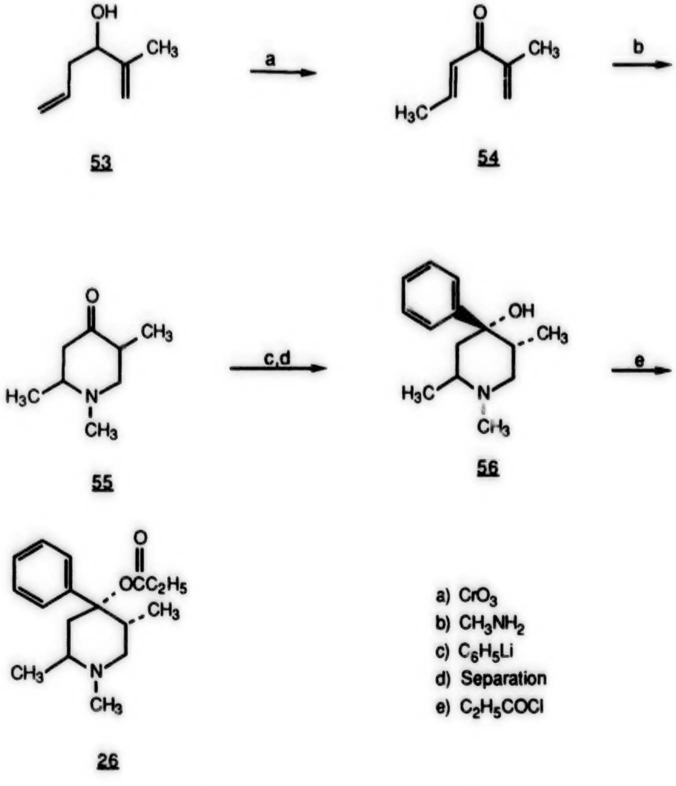
51



52

The preparation of the various dimethyl substituted prodine analogues is also carried out via the 4-piperidone route. This is illustrated in Scheme 11 by the synthesis of the 2,5-dimethyl compound trimeperidine (*26*) (Fries and Portoghese, 1974). Oxidation of (*53*) with chromium trioxide gives the ketone (*54*). Subjection of (*54*) to Michael condensation with methylamine yields the intermediate 4-piperidone (*55*). Addition of phenyllithium to (*55*) provides a mixture of diastereoisomeric alcohols which are separated to give the desired γ-isomer (*56*). Propionylation with propionyl chloride gives (*26*).

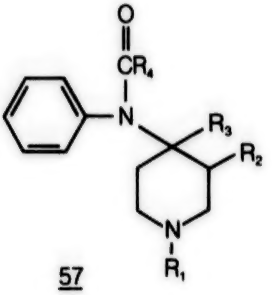
Scheme 11



a) CrO_3
b) CH_3NH_2
c) C_6H_5Li
d) Separation
e) C_2H_5COCl

Synthesis of Fentanyl Analgesics

Of the four classes of piperidine analgesics, the fentanyl class has provided the most potent compounds. An enormous number of fentanyl analogues has been prepared, many of which are substantially more potent than morphine. A large number of fentanyl analogues has obtained clinical utility. Since the SAR of the fentanyl family is treated in another chapter, this subject will not be addressed here. However, for the purpose of this chapter compounds represented by the general formula (*57*) show potent analgesic activity.



57

R_1 = Arylalkyl or heteroalkyl
R_2 = Alkyl
R_3 = H, CO_2R or CH_2OR
R_4 = Alkyl, O-alkyl

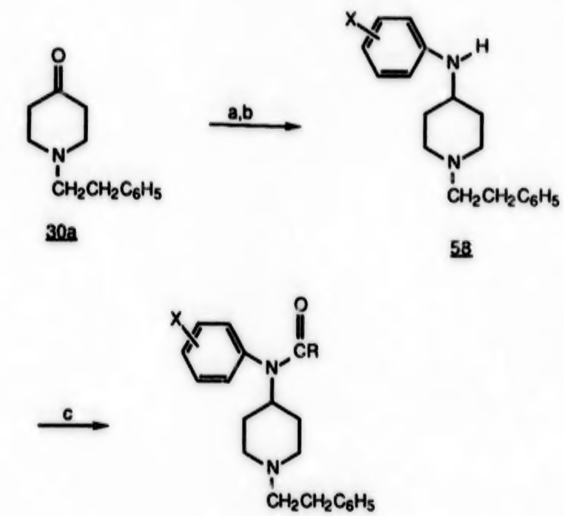
Beginning in 1981 when street samples of "China White" were identified as α-methylfentanyl (Kram *et al.*, 1981), an increasing number of fentanyl analogues has been identified as "designer drugs". The efforts to curb the abuse of fentanyl analogues have required authentic compounds as reference standards and for abuse liability studies. To date over twenty analogues have been synthesized for this purpose. Many of these analogues were compounds requested by DEA.

Fentanyl (*59a*) as well as a variety of analogues can be prepared utilizing the general synthetic route outlined in Scheme 12 (Casy *et al.*, 1969; Jonczyk *et al.*, 1978; Lobbezoo *et al.*, 1980; Lobbezoo *et al.*, 1981; Maryanoff *et al.*, 1982; Zee *et al.*, 1981). Condensation of commercially available 1-(β-phenethyl)-4-piperidone (*30a*) with aniline or substituted anilines followed by *in situ* sodium borohydride reduction of the intermediate imines gives the 1-(β-phenethyl)-4-anilinopiperidines (*58*) in good yield. Subsequent acylation of (*58*) provides the target compounds. Using this sequence analogues (*59b-59h*) were prepared without difficulty. In each case the acylation reaction with the appropriate anhydride was carried out.

The thioamide analogue (*60*) (cf. Scheme 13) was prepared by treatment of fentanyl base with Lawesson's reagent (p-methoxyphenylthionophosphine sulfide dimer) (Fieser, 1980; Pedersen *et al.*, 1978). This reaction is applicable to a variety of fentanyl analogues and could be used to convert controlled compound into a noncontrolled one.

Two additional synthetic routes to fentanyl (*59a*) are shown in Scheme 14. The first of these (Zee and Wang, 1980) utilizes 4-anilinopyridine (*61*) as the starting material (Route A). Treatment of (*61*) with propionic anhydride affords the amide (*62*). Subsequent alkylation with β-phenethyl bromide yields the pyridinium bromide intermediate (*63*). Hydrogenation over platinum oxide reduces the pyridine ring and cleaves the propionyl group, affording 1-(β-phenethyl)-4-anilinopiperidine (cf. Scheme 12; (*58*), X=H). A second propionylation reaction gives (*59a*).

Scheme 12



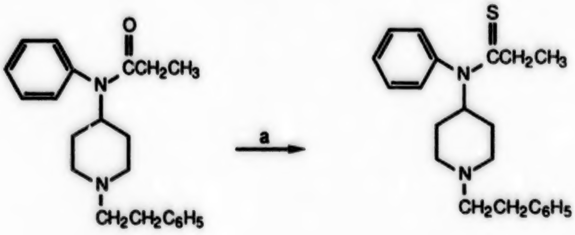
30a

58

59a : R = CH_2CH_3, X = H
59b : R = CH_3, X = H
59c : R = $(CH_2)_2CH_3$, X = H
59d : R = $CH(CH_3)_2$, X = H
59e : R = $(CH_2)_3CH_3$, X = H
59f : R = CH_2CH_3, X = p-CH_3
59g : R = CH_2CH_3, X = p-F
59h : R = CH_2CH_3, X = p-OCH_3

a) X–$C_6H_4NH_2$, p–TsOH
b) $NaBH_4$
c) RCOCl or $(RCO)_2O$

Scheme 13

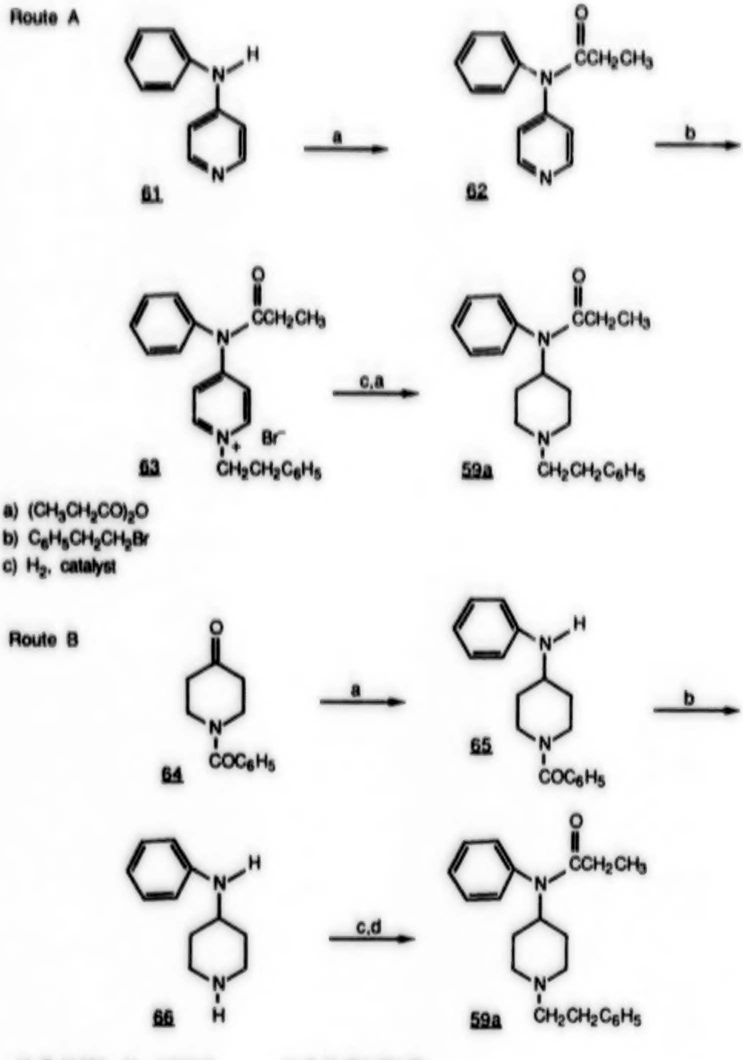


59a

60

a) Lawesson's reagent

Scheme 14



Route A:

a) $(CH_3CH_2CO)_2O$
b) $C_6H_5CH_2CH_2Br$
c) H_2, catalyst

Route B:

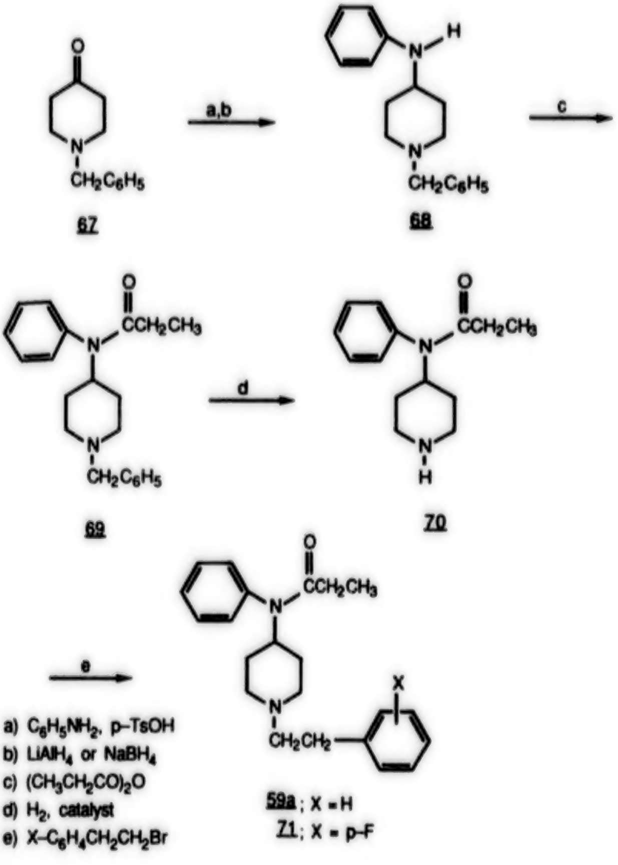
a) $C_6H_5NH_2$, H_2, catalyst
b) Hydrolysis
c) $C_6H_5CH_2CH_2Br$
d) $(CH_3CH_2CO)_2O$

Riley *et al.* (1973) used a similar approach to prepare a series of fentanyl analogues containing methyl substituents in the piperidine ring.

The reaction sequence illustrated in Route B makes use of commercially available 1-benzoyl-4-piperidone (*64*) (Zong *et al.*, 1979). Hydrogenation of (*64*) in the presence of aniline gives 1-benzoyl-4-anilinopiperidine (*65*) which is subjected to hydrolysis to obtain 4-anilinopiperidine (*66*). Subsequent treatment of (*66*) with β-phenethyl bromide followed by propionylation of the alkylation product yields fentanyl (*59a*). This four-step synthesis could also be used to prepare a variety of fentanyl analogues since variation of the aniline, β-phenethyl and acyl groups is possible.

The original synthesis of fentanyl (*59a*) is outlined in Scheme 15 (Janssen, 1964; Janssen, 1965). Commercially available 1-benzyl-4-piperidone (*67*) is converted to N-(1-benzyl-4-piperidyl)-N-phenylpropanamide (*69*) using conditions essentially identical to those illustrated in Scheme 12 for the corresponding 1-(β-phenethyl) compounds. Hydrogenolysis of (*69*) gives the versatile intermediate N-(4-piperidyl)-N-phenylpropanamide (*70*). Subsequent alkylation with β-phenethyl bromide affords (*59a*). Variation of the aniline, acyl and alkylating groups has allowed the preparation of a wide variety of fentanyl analogues (Janssen, 1965), of which one example is the p-fluoro analogue (*71*) (Hwang *et al.*, 1986; Janssen, 1965). This reaction sequence has been utilized to prepare the benzyl analogue (*69*) as well as N-(4-piperidyl)-N-phenylpropanamide (*70*).

Scheme 15



a) $C_6H_5NH_2$, p-TsOH
b) $LiAlH_4$ or $NaBH_4$
c) $(CH_3CH_2CO)_2O$
d) H_2, catalyst
e) $X\text{-}C_6H_4CH_2CH_2Br$

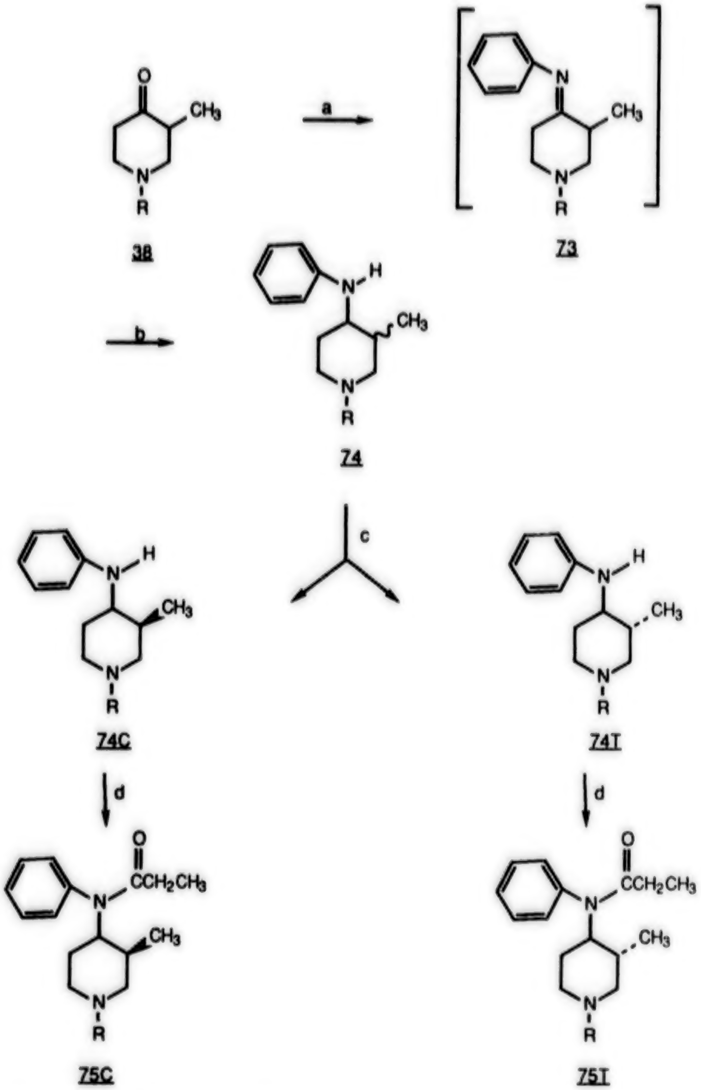
As illustrated by the examples in the above paragraph and elsewhere in this section, the fentanyl analogues have been named as amide derivatives. Other systematic methods are also available for naming these compounds. However, the use of a systematic nomenclature is preferable to the use of trivial names because the latter names are often inaccurate. A case in point is provided by the p-fluoro analogues (*59g*) (cf. Scheme 12) and (*71*) (cf. Scheme 15). Analogue (*59g*) is known as "p-fluorofentanyl" (Baum, 1985) and analogue (*71*) is called "fluorofentanyl" (Hwang, 1986). Neither name distinguishes one analogue from the other. Use of the names N-[1-(2-phenylethyl)-4-piperidyl]-N-(p-fluorophenyl)propanamide and N-[1-[2-(p-fluorophenyl)ethyl]-4-piperidyl]-N-phenylpropanamide for (*59g*) and (*71*) provides a clear distinction. Such distinctions could be extremely important in regulatory matters.

N-(4-piperidyl)-N-phenylpropanamide (*70*) (cf. Scheme 15) has been utilized as a starting material for the preparation of several fentanyl analogues having different substituents attached to the piperidine nitrogen. Both the structures of the analogues and the reagents used in the preparations are summarized in Table 1. The (2-thienyl)methyl chloride and 2-(2-thienyl)-ethanol tosylate were prepared by standard procedures, and the 1-(2-thienyl)-2-propanone was derived from 2-thiophenecarboxaldehyde using the nitroalkene route reported by Hass *et al.* (1950). The remaining reagents were commercially available. Four of the synthetic procedures involved displacement of halogen or tosyl in accordance with a general procedure (Janssen, 1965). The two reductive amination procedures took advantage of the selective reduction of the iminium moiety by cyanoborohydride at the appropriate pH (Borch *et al.*, 1971). The use of styrene oxide in the preparation of (*72f*) was based on a reported procedure (van Daele *et al.*, 1976). Analogues (*72c*) and (*72d*) (α-methylfentanyl) were previously prepared by Janssen (1965).

Introduction of a 3-methyl group into the piperidine ring of fentanyl is known to enhance analgesic activity with the cis diastereoisomer being approximately eight times more active than fentanyl (van Bever *et al.*, 1974). A general scheme for the preparation of some cis- and trans-3-methylfentanyl analogues is depicted in Scheme 16. Condensation of the (±)-1-arylalkyl-3-methyl-4-piperidones (*38*) (cf. Scheme 8, Route A) with aniline provides the intermediate imines (*73*) which are reduced in *in situ* to generate a mixture of (±)-cis- and (±)-trans-1-arylalkyl-3-methyl-4-anilinopiperidines (*74*) (Maryanoff *et al.*, 1982). Separation of the isomers followed by propionylation provides the cis (*75C*) and trans (*75T*) analogues. Starting with (±)-3-methyl-1-(β-phenethyl)-4-piperidone (*38*, $R=C_6H_5CH_2CH_2$), (±)-cis-3-methylfentanyl (*75C*, $R=C_6H_5CH_2CH_2$) and (±)-trans-3-methylfentanyl (*75T*, $R=C_6H_5CH_2CH_2$) were synthesized using this approach. Likewise, starting with (±)-1-benzyl-3-methyl-4-piperidone (*38*, $R=C_6H_5CH_2$) the corresponding benzyl analogues (*75C*) and (*75T*) ($R=C_6H_5CH_2$) were prepared. The cis:trans isomer ratio was approximately 2:1 in the β-phenethyl series and approximately 4:1 in the benzyl series. The 3-methylfentanyl analogues prepared via the 4-anilinopyridine route (*vide supra*) were exclusively the cis isomers (Riley *et al.*, 1973).

The isomer separation step shown in Scheme 16 also serves as a purification step. The condensation of (±)-3-methyl-1-(β-phenethyl)-4-piperidone (*38*, R=$C_6H_5CH_2CH_2$) with aniline does not go to completion. The unreacted ketone is reduced by sodium borohydride to a mixture of alcohols which contaminates the (±)-cis/trans-3-methyl-1-(β-phenethyl)-

Scheme 16



a) $C_6H_5NH_2$, p-TsOH
b) $NaBH_4$
c) Separation
d) $(CH_3CH_2CO)_2O$

4-anilinopiperidine (*74*, $R=C_6H_5CH_2CH_2$). If this material is used without purification, the mixture of alcohols is subsequently esterified in the propionylation reaction to give (±)-cis/trans-3-methyl-1-(β-phenethyl)-4-propionoxypiperidine. These isomeric esters are impurities in (±)-cis/trans-3-methylfentanyl which we prepared without the isomer separation step. It is suspected that these isomeric esters are among the impurities observed in street samples of 3-methylfentanyl.

By analogy to N-(1-benzyl-4-piperidyl)-N-phenylpropanamide (*69*) (cf. Scheme 15), hydrogenolysis of the benzyl analogues (*75C*) and (*75T*) ($R=C_6H_5CH_2$) is expected to provide intermediates useful for the synthesis of additional analogues. This was accomplished with the (±)-cis isomer to obtain (±)-cis-N-(3-methyl-4-piperidyl)-N-phenylpropanamide

Scheme 17

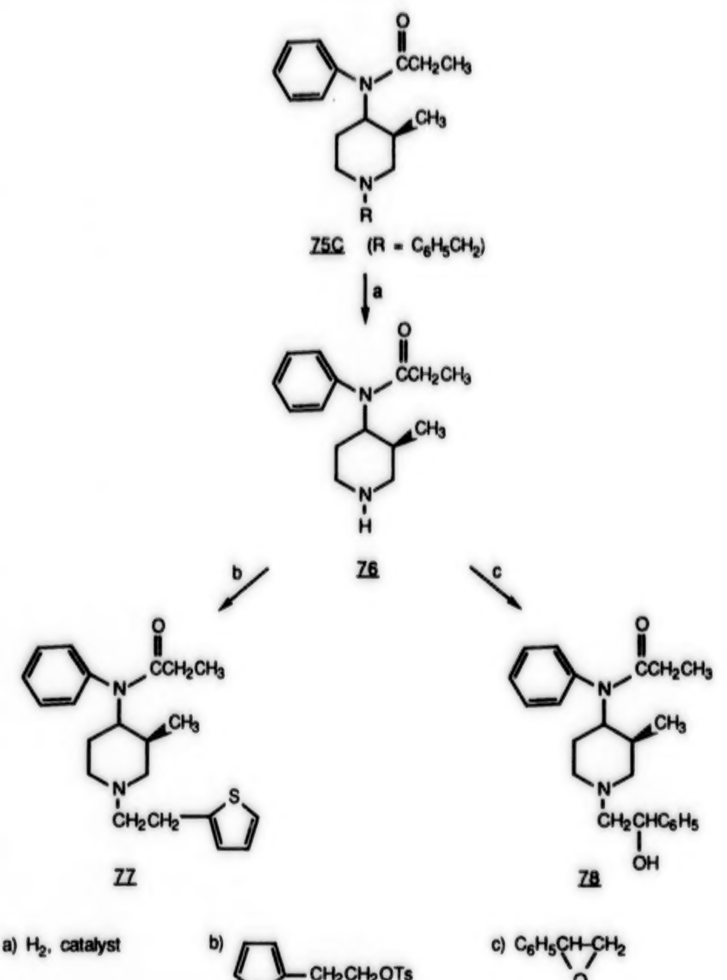
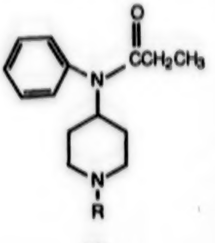
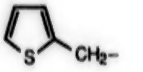
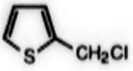
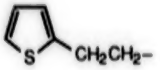
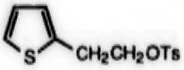
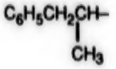
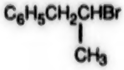
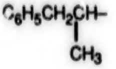
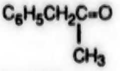
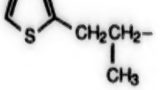
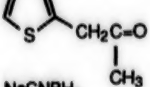
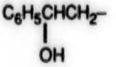
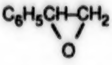


Table 1

Fentanyl Analogues Prepared from N-(4-Piperidyl)-N-phenylpropanamide (70)



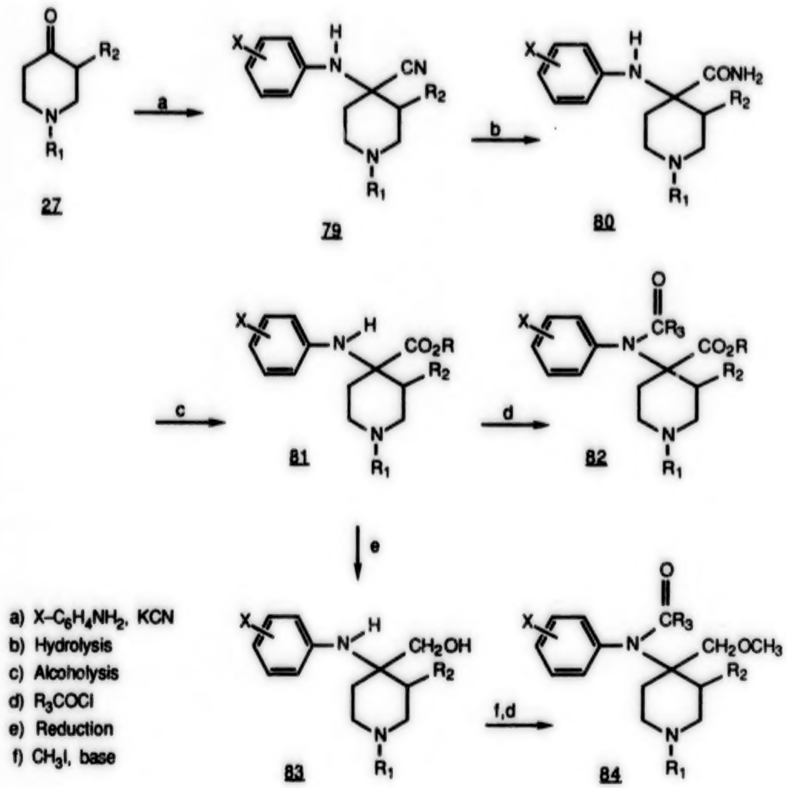
72

Compound No.	R	Reagent
72a	$C_6H_5CH_2CH_2CH_2-$	$C_6H_5CH_2CH_2CH_2Br$
72b		
72c		
72d	 $C_6H_5CH_2CH(CH_3)-$	 $C_6H_5CH_2CHBr(CH_3)$
72d	 $C_6H_5CH_2CH(CH_3)-$	 $C_6H_5CH_2C(=O)CH_3$ $NaCNBH_3$
72e		 $NaCNBH_3$
72f	 $C_6H_5CH(OH)CH_2-$	

(*76*) (cf. Scheme 17). From (*76*) (±)-cis-N-[1-[2-(2-thienyl)ethyl]-3-methyl-4-piperidyl]-N-phenylpropanamide (*77*) and (±)-cis-N-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide (*78*) have been prepared using procedures identical to those utilized to prepare analogues (*72c*) and (*72f*) (cf. Table 1). An alternative synthesis of (*78*) involves alkylation with 2-bromoacetophenone followed by sodium borohydride reduction (Zhu *et al.*, 1983).

Introduction of a substituent into the 4-position of the piperidine ring of fentanyl provides analogues with extremely potent analgesic activity and an unusually high safety margin (van Bever *et al.*, 1976; van Daele *et al.*, 1976). A general scheme for the preparation of these analogues is shown in Scheme 18. Reaction of the 4-piperidones (*27*) with the appropriate anilines and potassium cyanide leads to the anilinonitriles (*79*), which on hydrolysis give the amides (*80*). Alcoholysis affords the esters (*81*) which can then be acylated to give analogues of general structure *82*. Reduction of the esters (*81*) yields the carbinols (*83*). Subsequent methylation of the hydroxyl moiety followed by acylation yields the 4-methoxymethyl fentanyl analogues (*84*). If the starting 4-piperidones are substituted with benzyl at the 1-position (*27*, $R_1=C_6H_5CH_2$), hydrogenolysis of the benzyl group allows the introduction of other substituents at the 1-position. As the synthetic procedures outlined in Scheme 18 are no more difficult than those utilized for other fentanyl analogues, the high potency of the 4-substituted analogues could make them attractive targets for "designer drug" chemists.

Scheme 18



a) $X\text{–}C_6H_4NH_2$, KCN
b) Hydrolysis
c) Alcoholysis
d) R_3COCl
e) Reduction
f) CH_3I, base

References

Avison, A. W. D. and Morrison, A. L., Synthetic Analgesics. Part VI. The Synthesis of Ketobemidone, *J. Chem. Soc.*, 1469–1471 (1950).

Baum, R. M., New Variety of Street Drugs Poses Growing Problem, *Chem. Eng. News*, Sept. 9, 7–16 (1985).

Beckett, A. H., Casy, A. F. and Kirk, G., Alpha- and Beta-Prodine Type Compounds, *J. Med. Pharm. Chem.*, 1: 37–58 (1959).

Bell, K. H. and Portoghese, P. S., Stereochemical Studies on Medicinal Agents. 14. Relative Stereochemistries and Analgetic Potencies of Diastereomeric 3-Allyl and 3-Propyl Derivatives of 1-Methyl-4-phenyl-4-propionoxypiperidine, *J. Med. Chem.*, 16: 203–205 (1973).

Blicke, F. F., Faust, J. A., Krapcho, J. and Tsao, E., The Preparation of 1-Methyl-4-phenyl-4-cyanopiperidine, *J. Am. Chem. Soc.*, 74: 1844–1845 (1952).

Borch, R. F., Bernstein, M. D. and Durst, H. D., The Cyanohydridoborate Anion as a Selective Reducing Agent, *J. Am. Chem. Soc.*, 93: 2897–2904 (1971).

Casy, A. F., Hassan, M. M. A., Simmonds, A.B. and Staniforth, D., Structure-activity Relations in Analgesics Based on 4-Anilinopiperidine, *J. Pharm. Pharmac.*, 32: 434–440 (1969).

Casy, A. F. and Parfitt, R. T., Opioid Analgesics, Plenum Press, New York, NY, 1986, Chapters 6–8.

Fieser, M., Reagents for Organic Synthesis, Vol. 8, John Wiley and Sons, New York, NY, 1980, p. 327.

Fries, D. and Portoghese, P. S., Stereochemical Studies on Medicinal Agents. 18. Absolute Configuration and Analgesic Potency of Trimeperidine Enantiomers, *J. Med. Chem.*, 17: 990–993 (1974).

Hass, H. B., Susie, A. G. and Heider, R. S., Nitro Alkene Derivatives, *J. Org. Chem.*, 15: 8–14 (1950).

Hwang, D.-R., Feliu, A. L., Wolf, A. P., MacGregor, R. R., Fowler, J. S., Arnett, C. D., Holland, M. J., Carr, K. and Simon, E. J., Synthesis and Evaluation of Fluoridinated Derivatives of Fentanyl as Candidates for Opiate Receptor Studies using Positron Emission Tomography, *J. Labelled Compd. Radiopharm.*, 23: 277–293 (1986).

Jacobson, A. E., May, E. L. and Sargent, L. J., Medicinal Chemistry, 3rd ed., Burger, A., Ed., Wiley-Interscience, New York, NY, 1971, Chapter 49.

Janssen, P. A. J., Method for Producing Analgesia, U.S. Patent 3,141,823 (1964).

Janssen, P. A. J., 1-Aralkyl-4-(N-aryl-carbonylamino)piperidines and Related Compounds, U.S. Patent 3,164,000 (1965).

Johnson, M. R. and Milne, G. M., *Burger's Medicinal Chemistry*, 4th ed., Wolff, M. E., Ed., Wiley-Interscience, New York, NY, 1981, Chapter 52.

Jonczyk, A., Jawdosiuk, M. and Makoaza, M., Synthesis of the Analgesic Fentanyl on an Industrial Scale, *Przem. Chem.*, 57: 180–182

(1978).

Kram, T. C., Cooper, D. A. and Allen, A. C., Behind the Identification of China White, *Anal. Chem.*, 53: 1379A–1386A (1981).

Lenz, G. R., Evans, S. M., Walters, D. E. and Hopfinger, A. J., Opiates, Academic Press, Orlando, FL, 1986, Chapter 7.

Lobbezoo, M. W., Soudijn, W. and van Wijngaarden, I., Structure and Receptor Interactions of Morphinemimetics. Part 1. Hydroxy and Methoxy Derivatives of Fentanyl and Some Morphine Analogues, *Eur. J. Med. Chem.-Chim. Ther.*, 15: 357–361 (1980).

Lobbezoo, M. W., Soudijn, W. and van Wijngaarden, I., Opiate Receptor Interaction of Compounds Derived from or Structurally Related to Fentanyl, *J. Med. Chem.*, 24: 777–782 (1981).

Maryanoff, B. E., Simon, E. J., Gioannini, T. and Gorissen, H., Potential Affinity Labels for the Opiate Receptor Based on Fentanyl and Related Compounds, *J. Med. Chem.*, 25: 913–919 (1982).

McElvain, S. M. and Safranski, J. C., Jr., Piperidine Derivatives. XXIII. Certain Halogenated 1-Methyl-4-phenylpiperidines and Related Compounds. *J. Am. Chem. Soc.*, 72: 1334–1338 (1950).

Oh-Ishi, T. and May, E. L., N-Alkylnorketobemidones with Strong Agonist and Weak Antagonist Properties, *J. Med. Chem.*, 16: 1376–1378 (1973).

Pedersen, B. S., Scheibye, S., Clausen, K. and Lawesson, S. O., Studies on Organophosphorus Compounds. XXII. The Dimer of p-Methoxyphenylthiono-phosphine Sulfide as Thiation Reagent. A New Route to O-Substituted Thioesters and Dithioesters, *Bull. Soc. Chim. Belg.*, 87: 293–297 (1978).

Riley, T. N., Hale, D. B. and Wilson, M. C., 4-Anilidopiperidine Analgesics. I. Synthesis and Analgesic Activity of Certain Ring-Methylated 1-Substituted 4-Propananilidopiperidines, *J. Pharm. Sci.*, 62: 983–986 (1973).

Schmidle, C. J. and Mansfield, R. C., The Aminomethylation of Olefins. V. A New Synthesis of 4-Phenylpyridine and Related Compounds, *J. Am. Chem. Soc.*, 78: 1702–1705 (1956).

van Bever, W. F. M., Niemegeers, C. J. E. and Janssen, P. A. J., Synthetic Analgesics. Synthesis and Pharmacology of the Diastereoisomers of N-[3-Methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide and N-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide, *J. Med. Chem.*, 17: 1047–1051 (1974).

van Bever, W. F. M., Niemegeers, C. J. E., Schellekens, K. H. L. and Janssen, P. A. J., N-4-Substituted 1-(2-Arylethyl)-4-piperidinyl-N-phenylpropanamides, a Novel Series of Extremely Potent Analgesics with Unusually High Safety Margin, *Arzneim. Forsch.*, 26: 1548–1551 (1976).

van Daele, P. G. H., De Bruyn, M. F. L., Boey, J. M., Sanczuk, S., Agten, J. T. M. and Janssen, P. A. J., Synthetic Analgesics: N-(1-[2-Arylethyl]-4-substituted 4-Piperidinyl) N-Alkylalkanamides, *Arzneim. Forsch.*, 26: 1521–1531 (1976).

Zee, S.-H., Lai, C.-L., Wu, Y.-M., and Chen, G.-S., Preparation of Fentanyl from Phenethylamine and Methyl Acrylate, *K'o Hsueh Fa Chan Yueh K'an,* 9: 387–397 (1981).

Zee, S.-H. and Wang, W.-K., A New Process for the Synthesis of Fentanyl, *J. Chin. Chem. Soc. (Taipei),* 27: 147–149 (1980).

Zhu, Y.-C., Wu, R.-Q., Chou, D.-P. and Huang, Z.-M., Studies on Potent Analgesics. VII. Synthesis and Analgesic Activity of Diastereoisomers of 1-β-Hydroxy-3-methylfentanyl (7302) and Related Compounds, *Yaoxue Xuebao,* 18: 900–904 (1983).

Zong, R.-S., Yin, D.-X and Ji, R.-Y., Synthetic Studies on Potential Analgesics. II. Synthesis of Fentanyl, *Yao Hsueh Hsueh Pao,* 14: 362–367 (1979).

Illicit Synthesis of Phencyclidine (PCP), Lysergic Acid Diethylamide (LSD), Methaqualone and Their Analogues

Dr. A.W. Scaplehorn

In marked contrast to the USA and elsewhere, less than two dozen illicit laboratories come to police attention each year in the United Kingdom. In 1986 the total number was 15 with forensic science laboratories only being involved in about five. This is because ten were raided on the basis of information from the precursor monitoring program before synthesis was underway. The majority of these laboratories were synthesizing amphetamine in small quantities via the Leuckart Reaction.

The British drug scene is still very much based on cannabis, cannabis resin, amphetamine, heroin and LSD. The anticipated cocaine explosion has yet to occur although the drug is encountered, particularly in London. Other synthetic illicit drugs such as fentanyl, PCP, meperidine and their analogues fortunately have yet to make an appearance.

Phencyclidine (PCP)

Phencyclidine (PCP, Sernyl) is a popular drug of abuse in North America as well as being formerly used as a legitimate veterinary tranquilizer. The drug is related chemically to ketamine and is a potent analgesic and anaesthetic. Formerly given intravenously, PCP's severe adverse effects precluded its legitimate use and nowadays it is abused either by smoking (amounts of one to three milligrams applied to plant material), by nasal insufflation and intravenous injection (one to three milligrams) or by oral ingestion (two to six milligrams). These doses typically result in lethargy, disorientation, hallucinations, incoordination, catatonic rigidity, combativeness, etc. The adverse effects are widely reported.

Chemically PCP is 1-phenylcyclohexylpiperidine and a relatively simple molecule to synthesize. Analogues that have been prepared and have similar pharmacological effects included cyclohexamine (PCE) wherein the piperidine ring has been replaced with an ethylamino group. Phenylcyclohexylpyrrolidine (PHP) is the analogue in which the six-membered piperidine ring has been replaced with the five-membered pyrrolidine ring. Replacement of the cyclohexyl ring with a cyclopentyl gives phenylcyclopentylpiperidine (PCPP) and replacement of the phenyl with a thienyl group gives us thienylcyclohexylpiperidine (TCP). Clearly, there is scope for substitution in the various rings.

1-Piperidinocyclohexanecarbonitrile was produced initially in over 80 percent of the illicit syntheses of PCP investigated (Frank, 1983). This crystalline product is collected, washed and dried. It is then dissolved in a suitable solvent and reacted with phenylmagnesium bromide (Grignard reagent) for two to three hours. The reaction mixture is poured into an ice-ammonium chloride mixture which results in the formation of phencyclidine. Conventional chemistry is applied in order to extract, purify and recrystallize the product. No sophisticated equipment is needed and indeed in synthesizing the carbonitrile intermediate all one needs is piperidine and cyclohexanone together with either hydrochloric acid and sodium or potassium cyanide or sodium bisulfite and the cyanide salt.

Another method which was used in about 16 percent of the cases involved reacting piperidine and cyclohexanone in the presence of a catalytic amount of para-toluenesulfonic acid in benzene with the azeotropic distillation of water to form 1-(1-cyclohexenyl)piperidine as the tosylate salt which is then reacted with the Grignard reagent. Unlike the two previous syntheses, this route necessitates distillation as opposed to simple mixing in containers. The simple synthesis probably explains the popularity of PCP and its analogues in spite of the adverse behavioral and pharmacological effects they precipitate.

Lysergic Acid Diethylamide (LSD)

In contrast to PCP, LSD is a much more sophisticated molecule and its synthesis calls for a higher level of chemical skills.

LSD was first synthesized in the course of investigations on ergot alkaloids in the research laboratories of Sandoz at Basel, Switzerland, with the aim of producing further medically useful compounds. Hofmann's original report of his accidental ingestion of the drug in 1943 and of his resultant experiences have been widely published (Hoffmann, 1968). This led to systematic clinical studies by the psychiatrist Stoll of the Psychiatry Clinic at Zurich University. Since that time, several thousand papers on the drug's effects have appeared. In addition, a whole range of other lysergic acid derivatives have been synthesized and their pharmacological activities determined. Compounds wherein the diethylamide group has been replaced by other amide groups elicit psychic effects, but to a lesser degree than LSD.

The illicit chemist needs as starting material either an ergot alkaloid or lysergic acid or lysergamide. Smith's 'Psychedelic Chemistry' with the relevant references describes how to culture *Claviceps purpurea,* how to extract the alkaloids from woodrose seeds, and provides references to the complete synthesis of LSD. However, these routes seem most unlikely for significant illicit production so long as the ergot alkaloid or lysergic acid are obtainable. Routes to LSD from the acid include (1) conversion with lithium hydroxide to produce lithium lysergate followed by addition of a sulfur trioxide dimethylformamide complex to produce a lithium lysergate-sulfur trioxide complex; (2) reacting the acid with N,N-carbonyldiimidazole to produce the substituted imidazole, and, (3) reacting the acid with trifluoroacetic anhydride to produce the mixed anhydride of lysergic and trifluoroacetic acid. Each of these intermediates when reacted with diethylamine will produce LSD or using another amine a different amide.

The original route from an ergot alkaloid involves hydrolysis; most conveniently accomplished with hydrazine to produce the hydrazide which is subsequently converted to the azide with nitrous acid. Reaction of the azide with diethylamine will produce LSD. In all cases chromatography and crystallization are necessary to ensure a stable product.

In the Operation Julie case in the UK that led to the arrest of 120 people in March 1977, the manufacture of LSD started with ergotamine tartrate. Detailed information on the synthesis did not emerge; however, as evidenced by the recovered containers the N,N-carbonyldiimidazole route was used. It was estimated that two thirds of the world was supplied with LSD from these small but efficient laboratories operating either in London or Wales.

Methaqualone

Methaqualone (Quaalude [R]) is a quinazoline derivative that was first synthesized in 1951 and was found to be clinically effective as a non-barbiturate sedative and hypnotic. In the UK the proprietary preparation which also contained diphenhydramine was abused in the late 1960's and early 1970's but the problem ceased with its removal from the market. Methaqualone was not seen until recently as an adulterant in Asian heroin. Its source is thought to be diverted pharmaceutical material. Products with different substitution at the 3-position of the quinazoline moiety include mecloqualone where the group is o-chlorophenyl and nitromethaqualone where the group is o-methoxy-p-nitrophenyl. Both have similar pharmacological properties and neither has been encountered in the UK. Synthesis of these compounds is again relatively straightforward and involves no particular skills.

The most frequently used method involves the preparation of N-acetylanthranilic acid by reacting anthranilic acid with acetic anhydride. The N-acetylanthranilic acid is then refluxed with o-toluidine in toluene or in the case of other compounds, suitably substituted anilines with phosphorus trichloride or alternative catalysts such as phosphorus oxychloride, polyphosphoric acid or potassium bisulfate. A variation of this method involves heating solid N-acetylanthranilic acid and o-toluidine hydrochloride for a short period and another involves producing acetanthranil from anthranilic acid and reacting that with o-toluidine.

Additional methods may start from isatoic anhydride and 2-methyl-4-(3H)-quinazolinone.

References

Frank, R.S., The clandestine drug laboratory situation in the United States, *JFSCA*, 28(1): 18, 1983.

Hofmann, A., *Drugs Affecting the Central Nervous System,* Vol. 2, Editor A; Chapter 5, Burger, E. Arnold, London, 1968.

Smith, M.V., *Psychedelic Chemistry,* Loompanics Unlimited, Mason MI 48854, 1981.

Clandestine Production Processes for Cocaine and Heroin

Donald A. Cooper

Introduction

The use (abuse) of the coca leaf and the opium poppy is thought to have been practiced for at least thirty-four hundred years (Lathrap, 1976; Rosengarten, 1969). However, the abuse of chemically manipulated extracts of these plants is a relatively recent phenomenon, first starting around the turn of the last century. Over the years an enormous amount of research has been performed in an effort to understand the physiological effects resulting from the consumption of these plant products. A large proportion of this work has dealt with the principal alkaloidal constituent of these plants, i.e. cocaine from the coca leaf and morphine from the opium poppy. To the author's knowledge there is no work which addresses those health effects produced by the consumption of co-extractives and other chemical impurities which are present in the clandestinely produced product. It may be that some of these chemical impurities and/or co-extractives have a negative impact of significance upon the health of the user. As the abuse of any specific drug must ultimately result in an expenditure of funds for health care of the user, it follows that the presence and the nature of these co-extractives and chemical impurities in the drug will also have an effect upon national health costs.

The methods used today for the extraction and the conversion of the extracts to a street saleable commodity are of unknown origin, but most probably, these procedures are derived from published works in the scientific literature. It is known that, with relatively few exceptions, the individuals who practice these methods have either no or very little background in the sciences and often little formal education. This situation has resulted in the creation of an "art" that has been passed on from individual to individual in confidence. Consequently, information passed on to law enforcement officials about the actual procedures being used are almost never obtained from a trained professional, especially one who is sympathetic to law enforcement. Therefore, it is the case that the following accounts of these methods are in some parts speculative. However, the methods described in this article do represent a compilation from many information sources and it is felt that they are accurate.

Cocaine Production Perspective

There are two principal sources for the coca leaf, the Far East (Java, Ceylon, and Formosa) and South America. The Far Eastern leaves are typically quite low in cocaine content and are not known to be involved in the illicit market. The South American leaves come principally from Colombia, Peru, and Bolivia. There are two principal varieties; *Erythroxylon coca* Lamarck, and *Erythroxylon truxillense* Rusby. There is a third plant type originally thought to be a separate species (*Erythroxylon novogranatense* Hieron) but it is now considered to be identical to *Erythroxylon truxillense.* (Schulz, 1907; Plowman, 1979) The alkaloidal content of *Erythroxylon coca* grown in Bolivia is from one-half to one and one-half percent. A major proportion of the total alkaloidal content is cocaine. (DeJong, 1906)

The coca shrub used for the illicit production of cocaine is principally grown on the eastern slopes of the Peruvian and Bolivian Andes Mountains between an elevation of five hundred and two thousand meters. (Plowman, 1979) The shrub can grow to a height of four to five meters but it is usually pruned to approximately one and one-half meters. (Ashley, 1975) The first harvest takes place when the plants are from eighteen to twenty-four months old. The useful life expectancy of the coca plant is as long as fifty years, and the leaf can be harvested three or more times a year.

Cocaine was probably first isolated from leaves of the coca bush about 1855 by Gaedecke and referred to as "erythroxyline." However, it is Albert Niemann approximately five years later who is generally credited with the first isolation and naming of cocaine. (Ashley, 1975)

Cocaine from Natural Sources, Coca Paste Isolation

There are several methods that have been described as "the procedure" used by South American Indians for the isolation of alkaloids from dried coca leaf. Two of these methods are published in the open literature. Richard Ashley describes one whereby thirteen plus metric tons of leaves are processed in a single batch. (Ashley, 1975) Another is the procedure offered by Mortimer for small scale laboratory extractions. (Mortimer, 1901)

Over the course of years a number of non-scientists who claim to have observed the extraction process have been debriefed. Two procedures are consistently described, and they are given below as *A* and *B.* It is interesting that procedure *A* is quite similar to that described by Ashley whereas *B* bears a close resemblance to the procedure described by Mortimer. A third method, *C,* has been proposed by an independent laboratory. Validation of all three methods has been claimed. Of the three procedures described, we in this laboratory believe *B* to be the process most often employed.

A. 1.) The coca leaves are dampened [1] and are macerated until a paste is formed.

---

[1] It is not clear whether the water is actually added to the leaves or if it comes from transpiration of leaf cells.

2.) Sulfuric acid and additional water are added to the leaves, and the mixture is stirred.

3.) Kerosene is added and the mixture is stirred.

4.) After the phases separate, the aqueous phase is isolated from the mixture. (Several accounts specify drawing off the solution through a hole in the bottom of the container.)

5.) Ammonia, lime, sodium carbonate, or potassium carbonate is added to the aqueous phase to effect precipitation of the alkaloids.

6.) Filtration through cloth is generally specified for capturing the alkaloids.

B. 1.) To the leaves is added sodium or potassium carbonate and they are then dampened and macerated as in *A*–1.

2.) Kerosene is added and the mixture is stirred.

3.) The kerosene and leaves are separated.

4.) Sulfuric acid is added to the kerosene and mixed thoroughly.

5.) The aqueous phase is separated from the kerosene.

6.) Ammonia, lime, sodium carbonate, or potassium carbonate is added to the aqueous phase to effect precipitation of the alkaloids.

7.) The alkaloids are isolated through filtration.

C. 1.) The coca leaves are dampened and macerated with a carbonate as in *B*–1.

2.) Kerosene and water are added and the mixture stirred. The pH of the resulting solution is specified as 6.

3.) The aqueous phase is separated from the leaves and kerosene.

4.) Ammonia, lime, sodium carbonate, or potassium carbonate is added to the aqueous phase to effect precipitation of the alkaloids.

5.) The residue is captured by filtration.

The product obtained through any of these processes is thought to be at least fifty percent cocaine base and provides an overall yield of cocaine that is between two and eight tenths of a percent relative to dry leaf weight. The Indians call this product sulfato or coca paste.

Cocaine Base

The clandestine methods utilized in the production of cocaine base and cocaine hydrochloride from the crude coca paste are known with reasonable certainty. To date all information obtained indicates one principal procedure is being used and it is as described below.

1.) The crude coca extract (sulfato) is dissolved in dilute sulfuric acid.

2.) Dilute potassium permanganate is added [2] and the solution filtered.

3.) Ammonia is added to precipitate the cocaine base.

---

[2] Some lab operators are known to add ice along with the permanganate so as not to "burn" the cocaine.

4.) The cocaine base is captured by filtration and dried.

Cocaine Hydrochloride

5.) Dry cocaine base is dissolved in ethyl ether and filtered.

6.) A mixture of hydrochloric acid and acetone is added to the ethyl ether solution.

7.) The cocaine hydrochloride is recovered via filtration.

8.) The filtered residues are dried and packaged.

In nearly all accounts of the "cocaine base process", considerable point is made of the addition of potassium permanganate as described above in step (2). It is thought that cinnamoylcocaine is much more susceptible to permanganate oxidation than is cocaine (DeJong, 1948), and we have accepted that as the rationale for its use. However, the cinnamoylcocaines are found in a large proportion of illicit cocaine samples. This suggests either that permanganate use may not be as widespread as our intelligence reports suggest, or that these procedures do not oxidize the cinnamoylcocaines to any significant extent.

Cocaine from Total Synthesis

In 1917 Robinson published the synthesis of tropinone and thereby provided a method for producing the basic ring structure of the cocaine molecule. However, it was Willstätter in 1923 who first accomplished the total synthesis of cocaine. Since that time numerous groups have synthesized various tropane derivatives using modifications of Willstätter's work. (Findlay, 1953, 1954, 1957, 1959; Menzies and Robinson, 1924; Mannich, 1934; Schopf and Lehmann, 1935; Keagle and Hartung, 1946; Ziele and Schultz, 1950; Ziegler and Wilms, 1950; Bazilevskaya *et al.*, 1958; Sinnema *et al.*, 1968; Preobazhenskii *et al.*, 1936; Wallingford *et al.*, 1941; Allen *et al.*, 1981; Casale, 1987). The synthesis involves a Mannich condensation with methylamine, succinic dialdehyde, and the monomethyl ester of beta-ketoglutaric acid. The condensation product is then reduced with sodium amalgam and that product is benzoylated. If isomer resolution is not accomplished the product obtained is a mixture of racemic cocaine and racemic pseudococaine. Recently, work has been published which describes optimized conditions for the synthesis of cocaine via the Mannich reaction. (Casale, 1987) This work suggests that, starting with the Mannich condensation and going to final product, an overall yield for the cocaine isomers of approximately 25% can be achieved. Although this synthesis has been attempted in several clandestine laboratories it seems unlikely that it will become commonplace.

The synthesis requires a degree of expertise not normally found in the clandestine chemist and under optimum conditions 275 gm of sodium amalgam are required for each gram of final product produced.

Several other procedures for the synthesis of tropane alkaloids have been published. (Kashman and Cherkez, 1972; Tufariello and Mullen, 1978; Tufariello *et al.*, 1978, 1979; Hayakawa *et al.*, 1978; Noyori *et al.*, 1974; Petersen *et al.*, 1984). These procedures have neither been found in a clandestine operation nor have they been evaluated as to their possible use in such a setting.

Chemicals Required for Clandestine Cocaine Production

The following is a list of chemicals which have been *documented* as having been used in the clandestine production of cocaine from the coca shrub: potassium carbonate, potassium permanganate, sodium carbonate, sodium hydroxide, ammonium hydroxide, sodium bicarbonate, calcium oxide, calcium chloride, sulfuric acid, hydrochloric acid, water, kerosene, benzene, gasoline, ethyl ether, ethanol, methyl ethyl ketone, and acetone.

The total synthesis of cocaine and its isomers (cocaines) via a Mannich condensation requires the use of standard laboratory facilities and reagents. Hence, several of the compounds listed above would be required. In addition the following chemicals are required either as primary precursors or essential reagents: 2,5-dimethoxy-tetrahydrofuran, beta-ketoglutaric acid, methylamine, metallic mercury, metallic sodium, and benzoyl anhydride or a benzoyl halide.

Alkaloidal Impurities in Cocaine

Until recently, in addition to cocaine, only nineteen alkaloids had been reported present in *E. coca.* The following is a listing of those alkaloids; cinnamoylcocaine *[3], cinnamoylecgonine, tropacocaine*, pseudotropine*, tropine, tropan-3[alpha],6[beta]-diol, benzoylecgonine*, methylecgonine, ecgonine*, alpha-truxilline*, beta-truxilline*, norecgonine, hydrine, hygroline, dihydocuscohygrine, cuscohygrine, choline, and nicotine. (El-Iman *et al.,* 1985; Evans, 1981; Willaman and Schubert, 1961) Methylecgonidine is also listed by Evans as occurring in the plant. However, the ease with which that compound can be formed from cocaine makes this a questionable assertion. Several additional alkaloids have been found in *E. coca* within the last few years. In part they are 3-[alpha]-benzoyloxytropan-6-[beta]-ol, 6-[beta]-benzoyloxytropan-3-[alpha]-ol, 3-phenylacetoxynortropan-6-ol, nortropacocaine, nortropinol and esters (El-Iman *et al.,* 1985), and the remaining nine isomers of the truxilline alkaloids (Moore *et al.,* 1987). It is interesting that norcocaine has not been identified in any *E. coca* species. Norcocaine is found in all illicit cocaine samples, albeit often at trace levels. This would suggest that norcocaine is produced via an oxidative process either through the presence of peroxides in processing solvents and/or the previously described use of potassium permanganate (Sadtler, 1929). N-formylcocaine has also been observed in several illicit cocaine samples by this laboratory. This compound is easily made by oxidation of cocaine with dilute potassium permanganate (Allen and Cooper, 1984).

---

[3] The alkaloids which are marked with an asterisk are those that are often found in illicit cocaine samples in quantities greater than a few tenths of a percent relative to the cocaine.

The synthesis of the cocaines via the procedures of Findlay produced significant quantities of three impurities often noted in the final product (Cooper and Allen, 1984). Synthetic products obtained from clandestine operations have also contained these same impurities. Specifically they are 3-benzoyloxy-2-carbomethoxy-tropidine,[4] 2-carbomethoxy-3-methylaminotropidine, and 3-benzoyloxytropidine.

Chemical Processing Impurities

The Drug Enforcement Administration at the present time has an ongoing study for the purpose of determining solvents used in the processing of illicit cocaine samples. The approach has been to identify those compounds having high volatility which are entrained in the powder matrix of the end product. The analytical techniques utilized for nearly all of this work have involved heating the sample within a closed container, sampling the headspace followed by analysis using capillary gas chromatography/mass spectrometry. (Kiser, 1984) The work does not provide quantitative data nor were minimum levels of detection established. Table 1 lists a recent compilation of results in order of the most to least frequently encountered compounds.

Table 1

Solvents Present in Powder Cocaine Samples

Compound	No. of times detected (831 samples)	Percent of total
1. Acetone	621	74.7
2. Methyl ethyl ketone	454	54.6
3. Benzene	398	47.9
4. Toluene	291	35.0
5. Alphatic hydrocarbons	286	34.4
6. Ethyl ether	280	33.4
7. Methylene chloride	156	18.8
8. Xylene	56	6.7
9. Mesityl oxide	30	3.6
10. Tetrachloroethylene	29	3.5
11. Miscellaneous	<10	<1.2

---

[4] (3-benzoyloxy-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene)

A more useful method of listing this data is to express it as the number of times solvent *b* is found in solvent *a*. Table 2 provides such a listing where the compounds listed on the horizontal axis are the reference compounds (solvent *a*) and the vertical axis represents solvent *b*.

Care must be taken when attempting to interpret the data in Table 2. This is in part because in those cases where multiple solvents were detected, the lack of quantitative data makes it impossible to ascertain which were the primary solvents. Despite this problem, three comments may be offered; 1) acetone is used whenever possible, 2) it appears that the use of benzene, aliphatic hydrocarbons, and methylene chloride in combination is common, and 3) the benzene being used is most probably and most often not a pure solvent.

In an effort to learn more about the origin of the benzene, six samples were analyzed by an expert in flammable accelerants analysis. (Martz, 1987) The analyses of these samples did not provide any data consistent with the presence of accelerants. Despite these negative findings, it is believed by a number of individuals that gasoline is the probable source of the benzene found in many of these samples.

Heroin Production Perspective

The immediate precursor of heroin is morphine, and morphine is, in turn, obtained from opium. Opium is the dried milky juice obtained from the ripe flower pods of *Papaver somniferum L.*

This plant is commonly referred to as the opium or oil poppy. Physically, opium is a dried latex which is secreted from incisions made in the poppy capsules while they are still in the green stage, generally three or more days after flowering. The major constituents of opium are plant

Table 2

Co-relation of Solvents Found in Powder Cocaine Samples

	Tabulation for [solvent *b*/solvent *a* X 100]						
Solvent *a*	**Acetone**	**MEK***	**C_6H_6**	**C_7H_8**	**HC***	**ETHER***	**CH_2Cl_2**
Solvent *b*							
Acetone	100.0	27.1	52.3	41.9	60.8	76.8	56.4
MEK*	19.8	100.0	30.1	48.4	29.4	19.3	33.3
C_6H_6	33.5	27.1	100.0	54.2	68.2	17.9	74.4
C_7H_8	19.6	31.1	39.7	100.0	37.4	10.4	30.1
HC*	28.0	18.5	49.0	36.8	100.0	12.1	44.2
ETHER*	34.6	11.9	12.6	10.0	11.9	100.0	13.5
CH_2Cl_2	14.2	11.5	29.1	16.5	24.1	7.5	100.0

*MEK = methyl ethyl ketone; HC = aliphatic hydrocarbons; ether = ethyl ether fragments, resins, sterols, triterpenoid alcohols, fatty acids and alcohols, polysaccharides, and more than thirty alkaloids. Morphine and noscapine [5] account for the major portion of the alkaloidal content as it is not uncommon for each to contribute ten plus percent to the weight of dried opium. Considerable quantities of the opium poppy are grown commercially for the plant alkaloids medicinal value, for the seed-extractable oil, and for foodstuffs. When obtained by cold press methods the poppy seed yields a white oil which is used, in part, as a salad oil and as a diluent in olive oil. A second hot pressing of the seed gives an oil which has good drying properties and is much used in oil paints and varnishes. The use of the poppy seed as a condiment in bakery goods is very widely practiced and in some parts of the world the seed cake left after pressing is also used as food.

The plant will grow in nearly any temperate region in the world with the quantity of rainfall and soil type being the major factors determining a suitable growing habitat. Proof for this is provided by the fact that poppy seed cultivation is known in Russia as far north as 55 degrees and in Argentina as far south as 40 degrees (Rosengarten, 1969). It is generally thought that opium content is highest in those plants grown in tropical or semi-tropical regions. The opium used for the production of heroin which enters the United States is produced principally in southeastern and southwestern Asia and central America.

Morphine was first isolated from opium in 1805 by Serturner, but it was not until 1874 that the synthesis of diacetylmorphine was reported. Another twenty-four years passed before the drug was produced commercially by the Bayer Company in Eberfeld, Germany. The Bayer Company gave this new drug and the name heroin. By the beginning of the twentieth century heroin was widely used as a substitute for codeine and morphine in the treatment of tuberculosis and other respiratory diseases. It was also about this time that heroin first appeared in China where it very quickly replaced opium for the purpose of smoking. A few years after the 1925 International Opium Convention, controls began to severely limit the supply of heroin from Europe and the clandestine manufacture of heroin began in China.

Isolation of Morphine from Opium

The scientific literature contains a number of publications which describe processes for the extraction of morphine from opium. The best known of these publications describes the following commercial processes: the Thiboumery and Mohr process, the Robertson-Gregory process, the Barbier process, the Heumann process, the Schwyzer modification of the Robertson-Gregory process, and the Merck process (Schwyzer, 1927 & 1931; Barbier, 1950; Heumann, 1957). Except for two cases, all of the clandestine operations known to this laboratory followed the major tenets of the Thiboumery and Mohr process. Very often a clandestine operation will employ some small part of a process other than that of Thiboumery and Mohr. However, these are almost always concerned with improving the purity of the morphine after it has been isolated via the Thiboumery and Mohr process. Both of the cases where the Thiboumery and Mohr process was not used most probably involved the Robertson-Gregory process. Hence, only the Thiboumery-Mohr and the Robertson-Gregory processes are described in the following section. Included also is a description of those procedures which are taken from other processes for the purpose of further purification of the morphine.

---

[5] Also known as narcotine.

The Thiboumery and Mohr Process

Opium is dissolved in three times its weight of hot water and filtered.[6] The residue is re-extracted as above, and the filtrates are combined. The total filtrate volume is reduced to half and poured into a solution of boiling calcium hydroxide.[7] The precipitants, and in the case of the clandestine operation the insoluble materials from the first step, are filtered off. The captured residues are re-extracted with three parts of water and subsequently filtered. The filtrates are combined and the reextracted residues are removed from the process.[8] The total combined filtrates are concentrated to a weight approximately twice that of the opium and the solution is filtered.[9] The solution is brought to a boil and ammonium chloride is added. The solution is allowed to cool and then filtered to capture the morphine base. The morphine is dissolved in a minimum volume of warm hydrochloric acid. Upon cooling, morphine hydrochloride precipitates from solution and is isolated by filtration.

The Robertson-Gregory Process

The dried opium is exhaustively extracted with five to ten times its weight of cold water.[10] The solution is evaporated until a syrup is obtained and the syrup is re-extracted as above.[11] Insoluble materials are filtered off and the solution is evaporated until its density is 10° Baume. The solution is brought to a boil and calcium chloride is added. Then the solution volume is doubled with cold water and filtered. Once again, the solution is concentrated and filtered.[12] The solution is allowed to stand until such time that no further precipitate forms. The precipitate is separated from solution, dissolved in water, and the morphine re-precipitated with ammonia.

---

[6] The clandestine operator does not separate the insoluble materials, rather they are carried through to the next step.

[7] Reduction of the solution volume is usually not performed in clandestine operations and the caustic base is generally added to the filtrate in solid form immediately following the addition of opium to the hot water.

[8] Some clandestine operators are known to repeat this reextraction process up to seven times.

[9] This concentration step is generally not performed in the clandestine laboratory.

[10] In our reports hot water is specified.

[11] This step is apparently not performed in the clandestine process.

Miscellaneous Morphine Purification Processes

The following is taken from the Barbier process: Morphine base is placed in water at 80° C and tartaric acid is added until the solution becomes acid to methyl orange. The solution is cooled, and morphine precipitates as the bitartrate salt. The precipitate is recovered by filtration, washed with water, and dried. The morphine bitartrate is dissolved in hot water and ammonia is added until the pH is approximately six. The resulting morphine monotartrate is treated with activated carbon black, sodium bisulfite, sodium acetate, and ammonium oxalate. A small amount of the morphine monotartrate is precipitated at intervals, with ammonia, in order to check the progress of the decolorization. When the precipitate is pure white the entire batch is precipitated, filtered, and dried.

The following is taken from the Schwyzer process: Morphine base is washed with acetone, in which it is insoluble, and then the morphine is re-crystallized from hot ethyl alcohol.

The following is taken from the Heumann Process: Morphine base is washed with trichloroethylene.[13] The morphine is further purified by washing it with cold 40 percent ethyl alcohol. This process also describes washing morphine base with aqueous acetone as an additional purification step.

In the field of clandestine opium extraction there is a great variance in the effort expended in producing a pure morphine. A product of high purity is, in general, made by those laboratories that produce morphine as the hydrochloride salt and where the morphine is the end product. In some cases the product is nearly of pharmaceutical quality. Conversely, in general, those laboratories that continue directly on to heroin and produce the intermediate morphine as the free base make a product that is quite impure.

Morphine Isolation—Heroin Synthesis

The procedure described below is typical of a laboratory where morphine base is the intermediate and, in this case, where the final product, heroin, is also the free base. This description is made with some authority as the entire operation was witnessed by the author.

---

[12] The clandestine process does not include filtration at this point and the solution is concentrated until it is a thick syrup.

[13] Morphine base is nearly insoluble in most alkyl halides.

The "chemist" who completed the following process did not measure a single item. Rather, the end points of each step of the operation were determined by sight, smell, feel, and taste.

1. A drum was placed over a source of heat, approximately 20 liters of water was added to the drum, and heat was applied until the water was at a near boil. Six to eight kilograms of opium were broken up by hand into pieces three to eight centimeters in diameter and added to the drum, along with additional quantities of water. The mixture was stirred until all of the opium was dissolved.

2. While maintaining near boiling conditions, lime (CaO) was added with stirring. When the proper quantity of lime had been added, heating was discontinued and the drum was allowed to stand, undisturbed, for 12 hours. Upon standing, a marc [14] settled to the bottom of the drum.

3. The contents of the drum were either dipped or siphoned into heavy cotton cloth sacks. When no more solution could be added to the sacks they were tied at the top, then squeezed and pressed until all possible fluids have been removed.

4. The marc was removed from the cotton sacks and placed in a second smaller container. Five to ten liters of water were added to the container and the contents heated to a near boil for 30 minutes with occasional stirring. The contents were placed in the cotton sacks and filtered as previously described. The liquid obtained from this process was added to the original calcium morphinate solution.

5. The filtered calcium morphinate solution and the liquid from the recycled marc were poured into a clean drum. Heat was applied until the solution steamed and then ammonium chloride was added with stirring. The solution was allowed to stand for approximately three hours, during which time the morphine base precipitated out of solution.

6. The mixture from *5.* was filtered as described previously except that a tightly woven cotton cloth was used instead of the coarsely woven cotton sacks.

7. The dark brown residue (morphine base) was placed in the sun to dry.

Of the total quantity of the principal alkaloids that are present in the opium, approximately 90% of the noscapine and papaverine, 70% of the thebaine, 50% of the codeine, and 5% of the morphine will be present in the marc after the first extraction. Repeated extractions of the marc with hot water, without a corresponding addition of lime, will result in additional quantities of these alkaloids being drawn into the aqueous phase. Upon addition to the lime/calcium morphinate solution these alkaloids will again become insoluble. However, no attempt was made to filter this solution a second time; therefore these alkaloids are carried along with the morphine into the acetylation step.

---

[14] The marc contained plant and mineral debris along with relatively large quantities of certain opium alkaloids.

At that point when the morphine base was dry, the synthesis of heroin was begun.

The conversion of morphine to heroin is accomplished with a near universal sameness. The approach is the addition of a large excess of acetic anhydride to the dried morphine and the application of heat to the resulting mixture. The only true variables involved are the composition of the reaction vessel, the temperature of the reaction, the length of time the reaction is held to elevated temperatures, and the salt form of the morphine. In many instances it may be that these variables are determined more by happenstance than by design.

1. The dried morphine base was placed into a small container and sufficient acetic anhydride was added to thoroughly cover the morphine. The mixture was stirred and heated until the morphine base was completely solubilized. The solution was brought to a near boil and maintained at that temperature for approximately thirty minutes.

2. The container and its contents were cooled briefly by placing the container into cool water. The contents were then poured into the water.

3. The resulting solution was filtered through a tightly woven cotton cloth and the residue discarded.

4. A second solution was made by adding sodium carbonate to water. The sodium carbonate solution was added to the heroin acetate solution until effervescence ceased. Heroin base precipitated from solution and settled to the bottom of the container. An additional quantity of material also separated from solution but it floated as a "scum" on the surface of the solution. The scum was carefully scrubbed between the hands until it also settled to the bottom of the container.

5. The resulting mixture was filtered through a tightly woven cotton cloth. The filtrate was discarded and the heroin base was placed in the sun for drying.

Analysis of the scum described above in step (4) has shown that it contains approximately equal quantities of heroin, noscapine and neutral by-products. Of the total number of structurally different neutral components present, the majority is amides. However, those neutral compounds present in greatest individual quantities did not contain a nitrogen function and are highly aromatic in character. Nearly all of the neutral compounds arise from the action of acetic anhydride upon the various alkaloids present in the starting material, and the alkaloids thebaine and noscapine produce, by a considerable margin, the bulk of these neutral compounds (Allen *et al.,* 1983).

Heroin base samples, obtained via the procedure described above, will be 50 to 70 percent heroin, 5 to 20 percent noscapine, 3 to 10 percent neutral by-products, and 2 to 8 percent acetylcodeine. Significant quantities of calcium carbonate are also present, as are small quantities of other opium alkaloids along with mineral and plant debris.

Heroin from Codeine

The small-scale conversion of codeine to morphine followed by acetylation to heroin has become a problem in some areas of the world, (Bedford *et al.*, 1987). There are several published procedures for the O-demethylation of codeine but only two have been found in clandestine laboratories (Rice, 1977; Rapoport *et al.* 1951). By far the most commonly used procedure is that described by Rapoport *et al.* Presently the use of this procedure is a significant problem in New Zealand where it is known as "homebake" (Bedford *et al.*, 1987). The apparent source of choice for the codeine is the "Codral Forte" tablet which contains aspirin, acetaminophen, caffeine, and 30 milligrams of codeine phosphate. The details of the methods used are as follows:

Method 1 (Rapoport et al., 1951)

1. Crush the tablet and reduce it to a fine powder. Extract the codeine phosphate with water and filter it through paper.
2. Add the filtrate to a separatory funnel with chloroform and sodium hydroxide. Separate the chloroform layer and evaporate to get the codeine base.
3. Add 3.5 gm anhydrous pyridine hydrochloride to 1.3 gm codeine base and heat until a red color develops.
4. Add the reaction mixture and water to a separatory funnel and add sodium hydroxide until the pH exceeds 10.
5. Shake against chloroform, separate the phases, and discard the chloroform.
6. Adjust the aqueous phase pH to 9 and filter the resulting precipitant through paper (residue is dark brown).
7. Place the filtrate into another container, adjust the pH to 8, and scratch the sides to initiate precipitation.
8. Allow the solution to stand for 5 minutes and filter through paper.
9. Place the morphine base in a spoon, add acetic anhydride to it, and heat the spoon until the acetic anhydride has evaporated.

The substance that remains in the spoon is described as "tarry." Water is added to the contents of the spoon and stirred to effect dissolution. The resulting solution is drawn into a syringe for sale and use.

Method 2 (Rice, 1977)

1. As in (1) and (2) of Rapoport's method except the chloroform is not evaporated.
2. The chloroform solution of codeine is added to a chloroform solution of boron tribromide and stirred briefly.

3. The reaction is quenched with ice and ammonium hydroxide, and the morphine base is captured by filtering.

4. As in step (9) of Rapoport's method.

Rice states in his article that yields as high as 90 percent can be achieved, but the typical clandestine operation will very likely have considerably lower yields.

Heroin from Total Synthesis

The complete synthesis of morphine was first accomplished by Gates and Tschudi in 1952 (see also Elad, 1954). However, if a practical synthesis of morphine exists it is that described by Rice in 1980 with modifications in 1982. This procedure, according to Rice, is "short and experimentally simple" and provides very reasonable yields. However, it entails a total of ten synthetic steps and, in my view, considerable synthesis expertise. This synthesis has not been encountered in a clandestine operation.

Chemicals Found at Clandestine Heroin Laboratories

The following chemicals have been found at operational heroin laboratories. As the reader scans this list he will note that all of the chemicals stipulated in the previous discussion of heroin production methods are present. Acetyl chloride, acetic anhydride, ethylidene diacetate, phthalic anhydride, ethyl alcohol, acetone, ethyl ether, methanol, chloroform, formamide, benzene, pyridine, methyl ethyl ketone, boron tribromide, sodium carbonate, sodium bicarbonate, calcium oxide, calcium hydroxide, sodium hydroxide, ammonium hydroxide, ammonium carbonate, monobasic potassium phosphate, di-sodium hydrogen orthophosphate, sulfuric acid, hydrochloric acid, anhydrous hydrogen chloride gas, nitric acid, tartaric acid, acetic acid, citric acid, pyrogallic acid, phenylacetic acid, iodic acid, boric acid, sodium sulfate, ammonium sulfate, calcium chloride, ammonium chloride, sodium chloride, stannous chloride, potassium permanganate, ferric chloride, mercuric chloride, sodium tetraborate, ammonium oxalate, sodium acetate, sodium thiosulfate, sodium bisulfite, sodium alginate, potassium iodomercurate, potassium iodide, silica gel, activated carbon, chromium trioxide, bromocresol green, methyl red, methyl orange, phenolphthalein, and congo red.

Alkaloidal Impurities in Heroin Samples

In some illicit heroin samples the presence of other alkaloids above one-half percent is limited to the presence of acetylcodeine and O^6-monoacetylmorphine. Conversely, it is also quite common for samples to contain a greater quantity of the other opium alkaloids than there is heroin. Nearly always, noscapine is the predominant alkaloidal impurity in these samples. Such samples will also contain considerable quantities of papaverine, codeine, and often meconine; however, thebaine and narceine are almost never detected. In the application of gas-liquid chromatographic quantification methodologies for heroin small amounts of three synthesis by-products are occasionally detected. Specifically they are acetylthebaol (Freund *et al.*, 1897) delta ^{16,17}-didehydroheroin (Allen *et al.*, 1983), and O^3-[1-(1-carbomethoxyethyl)]1-O^6-acetylmorphine (Cooper and Kram, 1986). Many other alkaloids are known to be present in opium but they are usually present at low levels relative to the morphine and are not usually detected in basic extracts of heroin samples.

Neutral and Acidic Heroin Impurities

This laboratory has been involved in the study of neutral and acidic components which are found in illicit heroin samples for a number of years. At this time spectral data have been acquired for 271 such neutral or acidic compounds. These materials can arise for two different reasons. The first of these occurs when the filtration of the opium marc is not properly performed or when the marc is added back to the morphine prior to the acetylation step. This results in the presence in the morphine isolate of plant sterols, triterpenoid alcohols, sugars, and fatty acids (Bentley *et al.*, 1955).

Also, the acid and neutral compounds may arise from the action of acetic anhydride with the various alkaloids present in a sample (Allen *et al.*, 1983). These neutral compounds include such compounds as triacetylnormorphine (TANM) (Klein, 1977), acetylthebaol,[15] and 3,6-dimethoxy-4,5-epoxyphenanthrene (Teer, 1978; Bernhauer and Fuchs, 1982). The origin of these compounds was determined to be the reaction of acetic anhydride on morphine in the case of TANM, and on thebaine for the latter two phenanthrene compounds (Freund *et al.*, 1897). Many of the amidic neutrals found in illicit heroin samples arise in part from the presence of suitable N-nor precursors, and from the reaction of acetic anhydride with the appropriate N-oxides. The presence of N-oxides in the morphine extractives has been documented thoroughly by others (Dietzel and Huss, 1928; Markovic *et al.*, 1954; Yeh and Lach, 1960, 1961, 1971; Robles and Wientjes, 1961). However, the fact that thebaine and tetrahydroisoquinoline alkaloids are converted to neutral products in very high yields by the action of hot acetic anhydride indicates the presence of alternate mechanisms (Allen *et al.*, 1983; Cooper *et al.*, 1983). Other workers have also reported similar reactions and offered mechanistic explanations (Max and Polonovski, 1927; Hayashi *et al.*, 1974; Ahond *et al.*, 1970; Kim, 1976). Although none of the tetrahydroisoquinoline alkaloids[16] are observed in a basic extract of heroin, several are observed in an acid-neutral extract as amides. A number of these amidic derivatives are thought to arise from the isoquinoline alkaloids, laudanosine and reticuline.

---

[15] 3,6-dimethoxy-4-acetyloxyphenanthrene.

[16] Narcotine is *not* classified as a tetrahydroisoquinoline alkaloid.

The quantity and identity of the neutral and acidic compounds found in an illicit heroin sample are a function of the relative alkaloidal content of the opium, the techniques used for extracting the morphine, the conditions used in acetylation, and the various purification procedures utilized (Moore, 1983; Moore *et al.*, 1984; Neumann and Gloger, 1982).

It may be that some of these neutral compounds are associated with certain health problems. The rather large quantities of phenanthrene derivatives present in some samples should be particularly suspect. Some of these phenanthrene derivatives are similar to those that have been implicated in the high incidence of esophageal cancer found in dross users in northeast Iran (Malaveille, 1982; Friesen, 1985). Table 3 provides quantitative values for some of these neutral compounds. The data was obtained from 77 samples which were seized in six different areas in the world. The values are shown as a single averaged value for each compound or class of compounds. The quantification data is given relative to the heroin content of each sample, thereby facilitating comparison between data sets.

Minimal Chemical Requirements for Clandestine Heroin Production

The minimal chemical requirements for processing opium to heroin are: opium, water, lime, a pH modifier, and an acetylating agent. In those areas of the world where the opium poppy grows, it may well be that the opium is the least difficult ingredient to acquire. However, with the exception of the acetylating agent, the remaining materials can be acquired from local sources almost any place in the world.

Acetylating Agents

Apparently the supplies of acetic anhydride are quite ample as is evidenced by the fact that it is seldom substituted, despite the ready availability of other acetylating agents, and the fact that DEA files contain information on only one operational clandestine acetic anhydride laboratory. The acetic anhydride laboratory was using two processes; (i) the proylysis of acetone to produce ketene which is then passed through acetic acid to give acetic anhydride, and (ii) the reaction of acetyl chloride with sodium acetate. This laboratory was estimated to have made 1,400 kilograms of acetic anhydride. Contrary to the foregoing, two impurities, erythro- and threo-O^3-[1-(carbomethoxyethyl)]-O^6-acetylmorphine, have recently been identified in a small number of heroin samples.

Table 3

Acidic and Neutral Impurities Found in Heroin Samples

No. of Samples	A	B	C	D	E	F	G	H	I	Origin
14	0.286	3.150	1.034	0.157	0.702	0.171	0.150	0.952	0.033	1
5	0.411	0.530	0.217	0.445	0.053	0.028	0.000	0.000	0.056	2
30	0.445	4.106	2.102	0.285	0.931	0.735	0.589	0.701	0.055	3
6	0.518	5.910	2.050	0.420	1.197	1.873	1.207	0.664	0.172	4
5	5.835	18.251	6.375	0.540	9.238	0.110	0.428	4.680	0.195	5
17	0.002	0.006	0.001	0.004	0.001	0.000	0.001	0.001	0.000	6

A = meconin; B = non-nitrogenous phenanthrenes; C = acidic phenanthrenes; D = N-acetylnormorphines; E = amides derived from noscapine; F = N-acetylnorlandanosine; G,H = amides thought to be from reticuline; I = amide thought to be from codamine. 1 = Pakistan; 2 = Mexico; 3 = Nigeria; 4 = India; 5 = Turkey; 6 = Thailand.

///

This impurity is found in samples when acetylation is accomplished using ethylidene diacetate.

Ethylidene diacetate is not the acetylating agent, but is first decomposed to acetic anhydride. The decomposition reaction is achieved by the application of heat in the presence of catalytic amounts of either sulfuric acid or zinc halide. In commercial acetylation processes the acetic anhydride would then be separated by distillation; however, it is unlikely that the clandestine chemist would do so. Certainly the impurity of O^3-[1-carbomethoxyethyl)]-O^6-acetylmorphine would not be present in samples if such distillation were accomplished.

Conclusion

Botanical, chemical, and processing information concerning the clandestine manufacture of cocaine and heroin has been described.

Law enforcement activities which are designed to make the production of clandestine drugs more difficult will ultimately affect the nature and quantity of the impurities present in the final product. Such a change in the composition of these impurities could result in either a negative or, although much less unlikely, a positive effect upon the health of the user. Hopefully, the information provided in this article may be useful in assessing previously unrecognized health risks to the user, and in assessing the associated health costs to the individual nations who must manage the sickness that comes from the use of these drugs.

References

Ahond, A., Cave, A., Kan-Fan, C., and Potier, P., Modification de la reaction de Polonovski: preparation d'un nouveau reactif de Mannich, *Bull. Soc. Chim. Fr.*, No. 7: 2707–2710, (1970).

Allen, A., Cooper, D., Kiser, W., and Cottrell, R., The Cocaine Diastereoisomers, *J. Forensic Sci.*, 26: 12–26, (1981). Allen, A. C., Moore, J. M., and Cooper, D. A., delta $^{16-17}$-Dehydroheroinium Chloride: Synthesis and Characterization of a Novel Impurity Detected in Illicit Heroin, *J. Org. Chem.*, 48: 3951–3954, (1983).

Allen, A. C., Cooper, D. A., Moore, J. M., Teer, C. B., Thebaine Rearrangements: Nonclassical D Ring Migrations, *J. Org. Chem.*, 49(19): 3462–3465, (1983). Allen, A. and Cooper, D., unpublished work, (1984).

Ashley, R., "Cocaine: Its History, Uses and Effects," St. Martin's Press, New York, p. 13, (1975); ibid, p. 20; pp. 190–191.

Barbier, A., The Extraction of Opium Alkaloids, *Bull. Narcotics*, 2(3): 22–29, (1950).

Bazilevskaya, G., Bainova, M., Gura, D., Dyumaev, K., and Preobazhenskii, N., Synthesis of Cocaine, *Izvest. Vyssh. Uch. Zave. Khim. I*

Khim. Tekn., 2: 75–81, (1958). Bazilevskaya, G. I., Gura, D. V., Bainova, M. S., Dyumaev, K. M., Sarycheva, I. K., and Preobrazhenski, N. A., Synthesis of Tropan-3[alpha]-ol and tropine, *Zhur. Obshchei Khim.*, 28: 1097–1105, (1958).

Bazilevskaya, N., Bainova, M., Dyumaev, K., and Preobrazhenski, N., Synthetic Studies in the Field of Isomeric Cocaines VI. Synthesis of Methyl Esters of Pseudoecgonine and ecgonine, *Zhur. Obshchei Khim.*, 30: 2088–2091, (1960); ibid, Synthetic Studies in the Field of Isomeric Cocaines, V. Synthesis of Methyl Esters of 3[alpha]-tropanol-2[beta]-carboxylic acid (alloecgonine), and 3[alpha]-tropanol-2[alpha]-carboxylic acid (pseudoalloecgonine), *Zhur. Obschei Khim.*, 30: 1458–1461, (1960).

Bedford, K. R., Nolan, S. L., Onrust, R., and Siegers, J. D., The Illicit Preparation of Morphine and Heroin from Pharmaceutical Products Containing Codeine: "Homebake" Laboratories in New Zealand, *Forensic Sci. Internat.*, 34: 197–204, (1987).

Bentley, H. R., Henry, J. A., Irvine, D. S., Mukerji, D., and Spring, F. S., Triterpenoids. Part XXXII. Cyclolaudenol, a Triterpenoid Alcohol from Opium, *J.*, 596–602, (1955).

Bernhauer, D., and Fuchs, E., 4-O-Acetyl-3,6-dimethoxyphenanthren (Acetylthebaol) in illegalem Heroin, *Arch. Krim.*, 169 (3–4): 73–80, (1982).

Casale, J. F., A Practical Total Synthesis of Cocaine's Enantiomers, *Forensic Sci. Internat.*, 33: 275–298, (1987).

Cooper, D. A., Allen, A. C., and Moore, J. M., "Mass Spectral Identification of Neutral Impurities Found in Heroin Samples," Presented at the 31st Annual Conference on Mass Spectrometry and Allied Topics, Boston, MA, May 8–13, 1983; Cooper, D. A., and Allen, A. C., Synthetic Cocaine Impurities, *J. Forensic Sci.*, 29: 12–26 (1984); Cooper, D.A., and Kram, T., unpublished work, (1986).

De Jong, A. W. K., The Change in the Composition of the Cocaines in Java Coca Leaves During Their Growth. The acids of the esters of 1-nor-Ecgonine from Coca Leaves, *Rec. Trav. Chim.*, 67: 484–488, (1948); De Jong, A. W. K., The Alkaloids of Coca, *Rec. Trav. Chim. Pays-Bas*, 25: 233–237, (1906).

Dietzel, R., and Huss, W., Die Zersetzlichkeit des Morphins in wasseriger Losung insbesondere bei der Sterilisation, *Arch. Pharm.*, (Weinheim) 266: 641–667, (1928).

Elad, D., and Ginsberg, D., The Synthesis of Morphine, *J. Am. Chem. Soc.*, 76: 312–313, (1954).

El-Imam, Y. M. A., Evans, W. C., and Plowman, T., Alkaloids of Some South American Erythroxylum Species, *Phytochem.*, 24(10): 2285–2289, (1985)

Evans, W. C., The Comparative Phytochemistry of the Genus Erythroxylon, *J. Ethnopharm.*, 3: 265–277, (1981)

Findlay, S., The Structure of Anhydroecgonine Ethyl Ester, *J. Am. Chem. Soc.*, 75: 1033–1035, 1953 ibid, The Three-Dimensional Structure of Cocaine, *J. Am. Chem. Soc.* 75: 4624–4625, (1953) ibid, The Three-Dimensional Structures of the Cocaines. Part I. Cocaine and Pseudococaine, *J. Am. Chem. Soc.*, 76: 2855–2862, (1954) ibid, Concerning 2-Carbomethoxytropinone, *J. Org. Chem.*, 22: 1385–1394, (1957) ibid, The Three-Dimensional Structures of the Cocaines, II. Racemic Allococaine and Racemic Pseudoallococaine, *J. Org. Chem.*, 24: 1540–1550, (1959)

Freund, Michaels, and Gobel, Mittheilungen, *Chem. Ber.*, 30: 1357–1393, (1897)

Friesen, M., O'Neill, I. K., Malaveille, C., Garren, L., Hautefeuille, A., Cabral, J., Galendo, D., Lasne, C., Sala, M., Chouroulinkov, I., Mohr, U., Turusov, V., Day, N. E., and Bartsch., H., Mutation Res., Accepted for publication Feb. 20, 1985.

Gates, M., and Tschudi, G., The Synthesis of Morphine, *J. Am. Chem. Soc.*, 74: 1109–1110, (1952) ibid, 78: 1380–1393, (1956)

Hayakawa, Y., Baba, Y., Makino, S., and Noyori, R., General Synthesis of Tropane Alkaloids via the Polybromo Ketone-Iron Carbonyl Reaction, *J. Am. Chem. Soc.*, 100: 1786–1791, (1978)

Hayashi, Y., Nagano, Y., Honyo, S., and Teramura, K., Trapping an Intermediate of the Polonovski Reaction, *Tetrahedron Lett.*, No. 14: 1299–1302, (1974)

Kashman, Y., and Cherkez, S., Circular Dichroism of Heterocyclohexan-4-onic Systems-II. The Synthesis of the 8-Azabicyclo[3.2.1]Octanic System, *Tetrahedron*, 28: 155–165, (1972)

Keagle, L., and Hartung, W., Tropanone and its Homologs, *J. Am. Chem. Soc.*, 68: 1608–1610, (1946)

Kim, D. H., Acetic Anhydride as a Synthetic Reagent, *Reviews*, 13: 179–194, (1976)

Kiser, W. O., Drug Enforcement Administration—Miami, Florida, unpublished results, 1984

Klein, M., "Mass Spectrometry in Drug Metabolism (1977)", Analysis of Impurities in Illicit Heroin by Mass Spectrometry, Mass Spectrometry in Drug Metabolism, Ed. A. Frigerio and E. Ghisalberti, Plenum Publishing Co., NY, NY, 449–463, 1977

Lathrap, S. W., Ancient Ecuador Culture, Clay and Creativity, 3000–300 B.C., 1976, Chicago Illinois: Field Museum of Natural History

Malaveille, C., Friesen, M. Camus, A.–M., Garren, L., Hautefeuille, A., Bereziat, J. C., Ghadirian, P., Day, N. E., and Bartsch, H., Mutagens produced by the pyrolysis of opium and its alkalids as possible risk factors in cancer of the bladder and oesophagus, *Carcinogenesis*, 3(5): 577–585, (1982)

Mannich, C., Uber offenes Ekgonin und Tropin, *Arch. Pharm.*, 272: 323–359, (1934)

Markovic, O., Molnar, L., and Tomko, J., Determination of oxydimorphine in the presence of morphine, *Chem Zvesti*, 8: 580–582, (1954)

Martz, Roger, Special Agent, Laboratory Division, Federal Bureau of Investigation, personal communication.

Max, M. M., and Polonovski, M., Sur les aminoxydes des alcaloides (II), *Bull. Soc. Chim. Fr.*, 41, No.116: 1186–1190, (1927) ibid, Sur les aminoxydes des alcaloides. III. Action des anhydrides et chlorures d'acides organiques. Preparation des bases nor, *Bull. Soc. Chim. Fr.*, 41, No. 117: 1190–1208, (1927)

Menzies, R. C., and Robinson, R., Synthesis of Pseudo-pelletierine, *J. Chem. Soc.*, 125: 2163–2172, (1924)

Moore, J. M., Detection of Selected Heroin Manufacturing Impurities using Fused-silica Capillary and Electron Capture-Gas Chromatography, *J. Chromatogr.*, 16(223): 355–361, (1983) Moore, J. M., Allen, A. C., and Cooper, D. A., Determination of Manufacturing Impurities in Heroin by Capillary Gas Chromatography with Electron Capture Detection after Derivatization with Heptafluorobutyric Anhydride, *Anal. Chem.*, 56(4): 642–646, (1984) Moore, J. M., Cooper, D. A., Lurie, I. S., Kram, T. C., Carr, S. M., Harper, C., and Yeh, J., Gas Chromatographic Determination of Coca Leaf-Related Impurities in Illicit Cocaine, submitted to *J. Chrom.*, July 1987

Mortimer, W. G., "Peru: History of Coca", Vail & Co., New York, pp 311–312, (1901)

Noyori, R., Baba, Y., and Hayakawa, Y., A New, General Synthesis of Tropane Alkaloids, *J. Am. Chem. Soc.*, 96: 3336–3338, (1974)

Neumann, H. and Gloger, M., Profiling of Illicit Heroin Samples by High-Resolution Capillary Gas Chromatography for Forensic Application, *Chromatographia*, 16: 261–264, (1982)

Petersen, J., Toteberg-Kaulen, S., and Rapoport, H., Synthesis of (+ −)-[omega]-Aza[x.y.1]bicycloalkanes by an Intramolecular Mannich Reaction, *J. Org. Chem.*, 49: 2948–2953, (1984)

Plowman, T., Botanical Perspectives on Coca, *J. Psych. Drugs*, 11(1–2): 103–117, 1979)

Preobazhenskii, N. A., Schtschukina, M. N., and Lapins, R. A., Cocain-Synthese aus Hyoscyamin, I. Mittel.: Darstellung von Tropinon-carbonsaure-ester, *Chem. Ber.*, 69(7): 1615-1620, (1936)

Rapoport, H., Lovell, C. H., Tolbert, B. M., The Prepartion of Morphine-N-methyl-C^{14}, *J. Am. Chem. Soc.*, 73: 5900, (1951)

Rice, K. C., A Rapid, High-Yield Conversion of Codeine to Morphine, *J. Med. Chem.*, 20(1): 164–165, (1977) *ibid*, Synthetic Opium Alkaloids and Derivatives. A Short Total Synthesis of (+ −)-dihydrothebainone, (+ −)-dihydrocodeinone, and (+ −)-Nordihydrocodeinone as an Approach to a Practical Synthesis of Morphine, Codeine, and Congeners, *J. Org. Chem.*, 45(15): 3135–3137, (1980) *ibid*, Synthetic Opium Alkaloids and Derivatives II. Efficient Total Synthesis of (-)-dihydrocodeinone and Congeners, Presented at the Proceedings of the Committee on Problems of Drug Dependence, 1982

Robinson, R., Synthesis of Tropinone, *J. Chem. Soc.*, 111: 762–776, (1917)

Robles, M.A. and Wientjes, R., Chromatographic and Spectrophotometric studies on the decomposition of sterilized Alkaloid Salts, *Pharm.*

Weekbl., 96: 379-387, (1961)

Rosengarten, F., "The Book of Spices", Livingston Publishing Company, Philadelphia, PA., 369-372, (1969)

Sadtler, S. P., Cocaine, IN: Allen's Commerical Organic Analysis, The Vegetable Alkaloids, Revised N. Evers, Ed. C. A. Mitchell, pp 528, (1929)

Schopf, C., and Lehmann, G., Die Synthese des Tropinons, Pseudopeeetierins, Lobeanins und Verwandter Alkaloide unter physioloischen Bedingungen, *Annalen,* 518: 1-36, (1935)

Schwyzer, J., Die Fabrikation der Alkaloids, Julius Springer, Berlin, pp 31-45, (1927) *ibid,* Die Fabrikation Pharmazeutischer und Chemisch-technischer Produkte, Julius Springer, (1931)

Schulz, O. E., Erythroxylaceae. In: Engler, A. (Ed.), *Das Pflanzenreich,* 4(134): 1-164, (1907)

Sinnema, A., Maat, L., Van Der Gugten, and A., Beyer, H., Configuration and Conformation of all Four Cocaines from NMR Spectra, *Rec. Trav. Chim., Pays-Bas,* 87: 1027-1041, (1968)

Teer, C. B., Drug Enforcement Administration—Dallas, Texas, unpublished results, 1978

Tufariello, J., and Mullen, G., A Synthesis of dl-Cocaine Using Nitrone Intermediates, *J. Am. Chem. Soc.,* 100: 3638-3639, (1978) Tufariello, J., Tegeler, J., Wong, S., and Ali, A., *Tetrahedron Lett.,* 20: A Stereo-specific Synthesis of (+−)-Cocaine, 1733-1736, (1978) Tufaiello, J., Mullen, G., Tegeler, J., Trybulski, E., Wong, S., and Ali, A., Synthesis in the Tropane Class of Alkaloids. Pseudotropine and dl-Cocaine, *J. Am. Chem. Soc.,* 101:2435-2442, (1979)

Wallingford, V., Homeyer, A., and Jones, D., Alkyl Carbonates in Synthetic Chemistry. II. Condensation with Ketones. Synthesis of beta-Keto Esters, *J. Am. Chem. Soc.,* 63: 2252-2254, (1941)

Willstätter, R., and Muller, W., Uber Tropylamine, *Chem. Ber.,* 31: 1202-1214, (1898) Willstätter, R., and Pfannenstiel, A., Uber Succinyldiessigsaure ester, *Annalen,* 422: 1-15, (1920) Willstätter, R., Bonner, M., Eine vollstandige Synthese von r-Ekgonin und von Tropinon, *Annalen,* 422: 15-35, (1921) Willstätter, R., Wolfes, D., and Mader, M., Synthese des Naturlichen Cocains, *Annalen,* 434: 111-139, (1923)

Yeh, S.Y. and Lach, J.L., Stability of Morphine in Aqueous Solution. I., *Amer. J. Hosp. Pharm.,* 17: 101-103, (1960) ibid, Stability of Morphine in Aqueous Solution II and III, *J. Pharm Sci.,* 50: 30-34, (1961) *ibid,* Stability of Morphine in Aqueous Solution IV, 60: 793-794, (1971)

Ziegler and Wilms, Das (Willstattersche) labile Cyclooctadein—(1,5), *Annalen,* 567: 31-43, (1950)

Ziele, K., and Schultz, W., Uber das dritte racemische Cocain, *Chem. Ber.,* 89: 678-679, (1950)

Stimulants and Hallucinogens: Structure and Stereostructure-Activity Relationships

Pedro A. Lehmann F., Ph.D.

Introduction

Pharmacologically active analogues, that is structural variants of a given psychoactive compound, are possible because the sites with which the brain's neurotransmitters (chemical messengers) interact are not totally specific in their recognition. That is, small molecular modifications in a false messenger are tolerated within certain limits. This is what makes possible the existence of analogues of abused or dangerous substances, which have been named "designer drugs." This term has been applied to compounds synthesized illicitly with the intention of circumventing the safeguards society has deemed necessary to place on certain abused drugs, the so-called controlled substances. In fact, drug design, when practiced licitly within academic or industrial establishments, is today one of the sources of newer and better drugs useful in treating a variety of deleterious conditions in man.

In the search for better (more potent and safer) drugs, the traditional approach taken by the medicinal chemist (also a drug designer) is to start with a lead structure having a given desirable pharmacological profile, and by slight, stepwise molecular modification followed by extensive bioassays, establish the pertinent structure-activity relationships (SAR). Over the last hundred years, experiences with dozens of different lead structures have shown that considerable latitude in their structures is permissible without loss of their characteristic pharmacological profiles. Although each drug family differs in detail, some general principles have been laid down which when applied systematically to a new drug class allow considerable modulation of the analogue's physico-chemical properties and pharmacological activity.

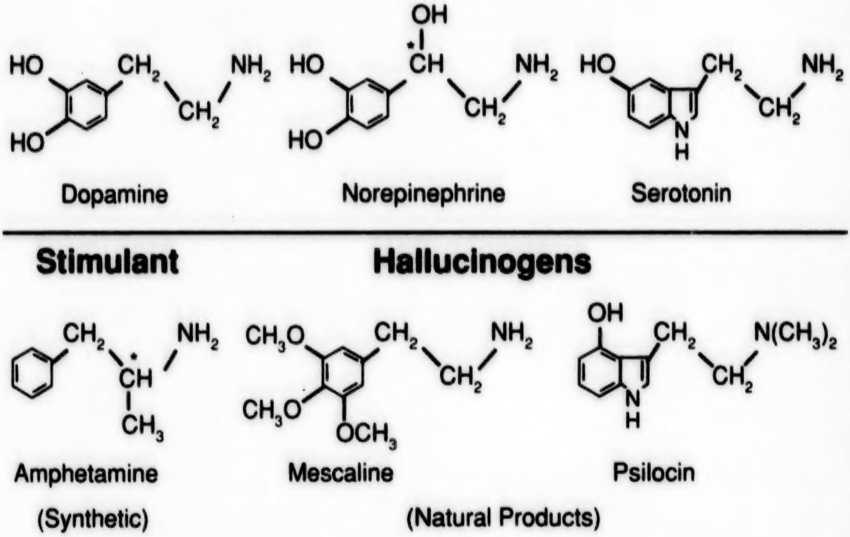
In this contribution some of these general principles will be explored and illustrated with examples from two important drug families: the central nervous system (CNS) stimulants and the hallucinogens (also called psychotomimetics).

Mode of Action

A glance at Figure 1 shows the close structural relationship between three neurotransmitters implicated in the action of stimulants and hallucinogens and that of three such compounds. This resemblance is certain-

Figure 1

CNS Neurotransmitters



Chemical structures of three pertinent CNS neurotransmitters and three prototype stimulants and hallucinogens. Chiral carbons, which are marked by an asterisk, result in the existence of enantiomers. Chemically dopamine, norepinephrine and mescaline are β-phenylethylamines, amphetamine is a β-phenylisopropylamine, and serotonin as well as psilocin are tryptamines.

ly responsible for the ability of the latter to masquerade as the former. The synthesis, release, presence, distribution and metabolism of these neurotransmitters in the brain presents a very complicated picture whose elucidation has been at the forefront of research in neurophysiology, neurochemistry and neuropharmacology for decades and will continue into the foreseeable future. It is generally accepted that normal brain function requires a minutely regulated balance of these neurotransmitters and that various types of modifications in their delicate homeostasis lead to profound alterations in brain function. Many useful drugs (anorectics, antidepressants, MAO-inhibitors, levodopa, etc.) have been developed which act by redressing such unbalanced states. Undoubtedly the mechanism of action of stimulants and hallucinogens is based on interference with the normal functions of one or several of these neurotransmitters. At present it is accepted that amphetamine and its derivatives are mixed-type sympathomimetic agents since they act both directly on norepinephrine receptors and by effecting its release from intracellular stores. The picture for hallucinogens is less clear and further confused by the fact that compounds with very different structures (LSD, bufotenine, myristicin, harmaline, ibogaine, etc.) also have this activity.

Structure-Activity Relationships

Two types of structural features play dominant roles in endowing analogues of these agents with activity:

1. Those which determine their lipid/water partitioning (lipophilicity and ionization) since they affect the analogue's entry into the brain.

2. Those affecting the spatial distribution (configuration and conformation) of the molecules since they determine the closeness of fit and thus their affinity for the receptor molecules they interact with.

Well over one hundred derivatives each of amphetamine and mescaline have been synthesized and tested in various bioassays. It is impossible to examine their SAR in depth (for this see the General Sources in the References) and this discussion will be limited to certain interesting and important features.

1. Stimulants

In a recent extensive review, Glennon (1987) described in detail the SAR of both the stimulants and hallucinogens. He considered the phenylisopropylamine structure (amphetamine itself) the point of departure from which both stimulating and hallucinogenic activity could be obtained by suitable molecular alteration. In general, substitutions on the aromatic ring reduce amphetamine-like activity; only N-methylation (methamphetamine) results in a potent stimulant. Increasing the size of the N-alkyl group greatly reduces this activity.

Among the important stimulants is cathinone, the active principle present in khat, obtained from the plant Catha edulis. It is simply β-ketoamphetamine. (S)-(-)-Cathinone is about ⅕th as potent as dextroamphetamine and some 5 to 10 times as potent as its enantiomer, (R)-(+)-cathinone.

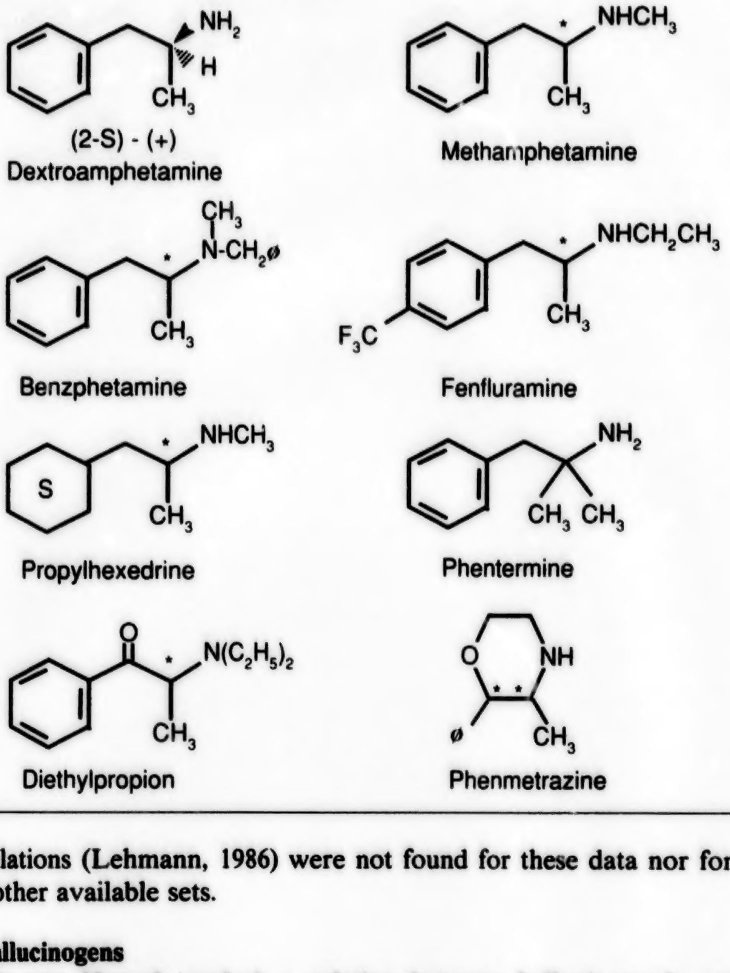
An extensive compilation (van Kammen *et al.*, 1984) is available on the activity of the amphetamine enantiomers in a large number of psychoactivity tests. From a SAR point of view, the stereoisomeric potency ratios are unusually small (range 1:1 to 10:1), dextroamphetamine usually being the more potent enantiomer. The low ratios indicate that the pertinent receptor or site of action displays low stereoselectivity.

In Figure 2 are shown the structures of dextroamphetamine and various analogues which are marketed as anorexigenic agents, i.e., with appetite suppressant activity. Although not entirely, this therapeutically desirable property generally goes hand in hand with the undesirable CNS stimulation. A considerable structural latitude is permitted provided the β-phenylisopropylamine moiety is contained in the structure.

With regard to absolute configuration, the data assembled in Table 1 indicate that enantiomeric amphetamines differ in potency as anorectics. The enantiomeric potency ratios (two to four fold) are surprisingly small in contrast with other psychoactive drug families, implying that in exerting their effect a loose binding to the receptor suffices. Eudismic-affinity

Figure 2

Structures of Some Marketed Anorectic Agents



correlations (Lehmann, 1986) were not found for these data nor for several other available sets.

2. Hallucinogens

In one Hansch analysis a relation between hallucinogenic activity and lipophilicity (Barfknecht *et al.,* 1975) was drawn. However, the analysis only explained 62% of the variance thus reflecting a large error in potency estimates as well as the fact that many partition coefficients were calculated and not measured.

The SAR of mescaline-like psychotomimetics has been summarized (Barfknecht *et al.,* 1978):

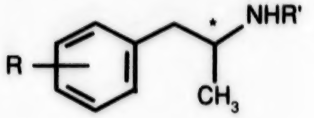
a) A methyl group on the α-carbon enhances potency, while smaller (hydrogen) or larger (ethyl) groups result in analogues which may be psychoactive but are not psychotomimetic.

b) In regard to substituents on the aromatic ring, three are better than one or two and the optimal substitution pattern is 2,4,5 (see Table 2).

Table 1

Anorectic Activity of Enantiomeric Amphetamines

(From Houlihan & Babington, 1981)



		ED50 MG/KG (RAT)			
R	R'	(+)	(-)	(±)	E.R.
H	H	2.8 ● x	6.4	4.3	2.3
4 - Cl	H	1.3 ● x	2.6	2.1	2.0
2, 4 - Cl_2	H	10.0	2.6 ● ?	4.1	3.8
3, 4 - Cl_2	H	4.0	1.8 ● ?	2.9	2.2
3 - CF_3	C_2H_5	2.8 ● x	10.0	5.2	3.6
3 - CF_3	CH_2CH_2OH	4.0 ● x	15.0	5.2	3.8

E.R.= Eudismic Ratio = Potency Ratio (Eutomer/Distomer)
● = Eutomer (More Potent Enantiomer)
x = (S) - Absolute Configuration
? = Absolute Configuration Unknown

c) Since these compounds are metabolized by modification at the 4-position (H>OH, CH_3O>OH), its blockage with methyl or halogen substituents yields more potent and longer lasting hallucinogens (*viz.* DOM and DOB, Table 3).

d) The N-methyl derivative of DOM is not psychotomimetic, but rather an antagonist.

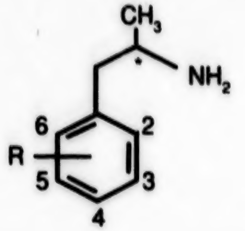
e) The presence of an α-methyl group leads to the separate existence of enantiomers; the (R)-(−) configuration, corresponding to that in LSD, is more potent than the (S)-(+) enantiomer.

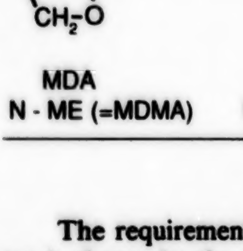
f) Distribution in the different phases of the body is strongly affected by a compound's water-lipid distribution, which in turn, is determined by the whole structure, including positional isomerism.

Some of the more interesting analogues are listed in Table 2. As shown, the number, position and size of the substituent on the aromatic ring influence the analogue's potency substantially. Particularly interesting are the two homologous series (4–R=alkyl or thioalkyl) which seem to indicate that ethyl or thioethyl are optimal, activity decreasing to either side.

Table 2

SAR of Hallucinogenic Phenylisopropyl Amines in Mescaline Units



				2, 5 - $(OCH_3)_2$	
R	M.U.	R	M.U.	4 - R	M.U.
4 - OCH_3	6	3, 4, 5 - $(OCH_3)_3$	2	CH_3	80
2, 4 - $(OCH_3)_2$	6	2, 4, 5 - $(OCH_3)_3$	20	CH_2CH_3	100
2, 5 - $(OCH_3)_2$	6	2, 3, 4 - $(OCH_3)_3$	<2	$CH_2CH_2CH_3$	80
3, 4 - $(OCH_3)_2$	1	2, 3, 5 - $(OCH_3)_3$	4	$CH_2CH_2CH_2CH_3$	40
2, 3, 4, 5 - $(OCH_3)_4$	6	2, 3, 6 - $(OCH_3)_3$	10	$CH_2CH_2CH_2CH_2CH_3$	10
		2, 4, 6 - $(OCH_3)_3$	10		
				S - CH_3	40
				S - CH_2CH_3	80
	3			S - $CH(CH_3)_2$	40
				S - $CH_2CH_2CH_3$	60
MDA					
N - ME (=MDMA)	0				

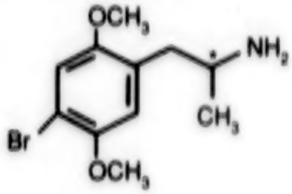
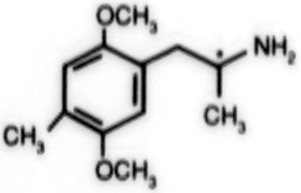
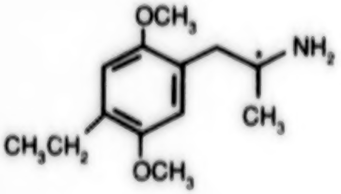
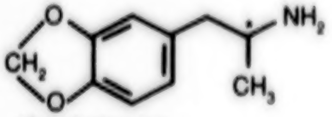
The requirement for high complementarity with the pertinent receptor is shown by the data presented in Table 3. The enantiomeric potency ratios range from three to ten fold, increasing with potency as has been found in many other series (Lehmann, 1986). In contrast to amphetamine derivatives where N-alkylation is tolerated, mescaline derivatives lose most of their potency when converted to $N-CH_3$ derivatives.

In contrast, in the tryptamine hallucinogens dialkylation to produce the N-methyl-N-iPr derivatives leads to substantial increases in potency as well as oral activity (Repke *et al.*, 1985).

Table 3

Relative Potencies of Some Enantiomeric Psychotomimetics

(From Anderson *et al*, 1978)

Structure	Name	Potency of RAC. Mescaline = 1	E.R.
	DOB	400	R/S = 10
	DOM	80	R/S = 4
	DOET	100	R/S = 4
	3, 4 - MDA	3	R/S = 3
(Amphetamine	———	——	S/R = 2)

Note: LSD 5R/5S > 20
E.R. = Eudismic Ratio = Potency Ratio (Eutomer/Distomer)

Conclusion

The stimulants and hallucinogens represent two drug classes with overlapping pharmacological profiles, especially at higher doses. Their relatively simple structures dictate easy syntheses. Furthermore, the fact that in chiral analogues both enantiomers display psychoactivity, resolution is often unnecessary thereby simplifying their production. The widespread amphetamine addiction patterns of the forties and fifties (Caldwell, 1980), which seemed to wane in the sixties and seventies, may again become prevalent. This possibility should be countered energetically by all concerned parties.

References

Anderson, III, G.M., Braun, G., Braun, U., Nichols, D.E. and Shulgin, A.T. in Barnett *et al.* (eds.), pp. 8–15, 1978.

Barfknecht, C.F., Caputo, J.F., Tobin, M.B., Dyer, D.C., Standridge, R.T., Howell, H.G., Goodwin, W.R., Partyka, R.A., Gylys, J.A., and Cavanagh, R.L. in Barnett, *et al.* (eds.), pp. 16–26, 1978.

Barfknecht, C.F., Nichols, D.E., and Dunn III, W.J., Correlation of Psychotomimetic Activity of Phenethylamines and Amphetamines with 1-Octanol-Water Partition Coefficients, *J. Med. Chem.* 18: 208–210, 1975.

Barnett, G., Trsic, M. and Willette, R.E. (eds.), Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists, and Hallucinogens, NIDA Research Monograph #22, U.S. Dept. of Health, Education and Welfare, Washington, D.C., U.S.A., 1978.

Caldwell, J. (ed.), Amphetamines and Related Stimulants: Chemical, Biological, Clinical, and Sociological Aspects, CRC Press, Boca Raton, Florida, 1980.

Cohen, S., The Psychotomimetic Agents, *Prog. Drug Res.* 15: 68–102, 1971.

Glennon, R.A., Psychoactive Phenylisopropylamines; in Meltzer, H.Y. (ed.), Psychopharmacology: The Third Generation of Progress, Raven Press, New York, 1987.

Houlihan, W.J., and Babington, R.G., Anorexigenics, in Wolff, M.E. (ed.), Burger's Medicinal Chemistry, 4th ed., Part III, pp. 1069–1108, John Wiley & Sons, New York, 1981.

Lehmann, F., P.A., Stereoisomerism and Drug Action, *Trends in Pharmacological Sciences* 7: 281–285, 1986.

Repke, D.B., Grotjahn, D.B. and Shulgin, A.T., Psychotomimetic N-methyl-N-isopropyltryptamines. Effects of Variation of Aromatic Oxygen Substituents, *J. Med. Chem.* 28: 892–986, 1965.

Shulgin, A.T., Hallucinogens, in Wolff, M.E. (ed.), Burger's Medicinal Chemistry, 4th ed., Part III, pp. 1109–1137, John Wiley & Sons, New York, 1981.

Schultes, R.E. and Hofmann, A., Plants of the Gods: Origins of Hallucinogenic Use, McGraw Hill, New York, 1980.

van Kammen, D.P., Ninan, P.T. and Hommer, D., Amphetamine Enantiomers: Psychopharmacological Effects, in Smith, D.F. (ed.) Handbook of Stereoisomers: Drugs in Psychopharmacology, CRC Press, Boca Raton, FL, 1984, pp. 297–315.

Structure-Activity Relationships of Morphinomimetics

J.P. Tollenaere, Ph.D.

Introduction

In 1913 P. Ehrlich stated that "corpora non agunt nisi fixata." Since that time, the concept of receptors has enjoyed a prominent place in our thinking about drug-receptor interactions and in discussions of the possible modes of action of drugs. Although receptors interacting with central nervous system (CNS) drugs have not yet been isolated, it is assumed that receptors are structural entities which do interact with drugs, leading to a drug-receptor complex. It is further thought that such a complex gives rise to a stimulus, which eventually leads to an experimentally observable pharmacological effect.

Because the three-dimensional structure of the receptor is lacking, one is forced to study the anatomy of the drug molecule supposedly acting on a particular receptor. Studying the stereochemical anatomy of drug molecules may lead to a classification of drugs based on their three-dimensional (3-D) characteristics. In doing so, one may come up with the so-called pharmacophoric pattern common to a given set of drugs or the essential chemical features necessary to elicit a pharmacological or biochemical effect. A pharmacophore may thus be defined as a 3-D pattern of atoms or groups of atoms in a well-defined mutual orientation that is necessary for the recognition of and interaction with a receptor.

Whereas in the past the classification of drugs was based on the classical two-dimensional representation of molecules – the so-called topological representation – today a large body of knowledge on the 3-D properties of drug molecules is available (Tollenaere *et al.*, 1979). In fact, with the almost routine application of X-ray diffraction techniques to small molecules, a wealth of information has been generated, and in this way, a precise account has been provided on the 3-D structure or the conformation of molecules in the solid state. Although it may be argued that the 3-D structure of a molecule, as observed in the solid state, is not necessarily identical to the 3-D structure in the vicinity of the receptor, it should be noted that the solid state conformation is a low-energy state and, therefore, a very probable structure.

In this paper, an outline will be presented on the main structural classes of morphinomimetics. For the purpose of this contribution, a morphinomimetic or narcotic analgesic is defined as a substance whose administration in animals is followed by a series of phenomena including: 1) relief or abolition of pain; 2) respiratory depression in all species; 3) excitement and Straub tail effect and mydriasis in mice; 4) lead pipe rigidity in rats. Morphinomimetics are further characterized by nalorphine or naloxone antagonism.

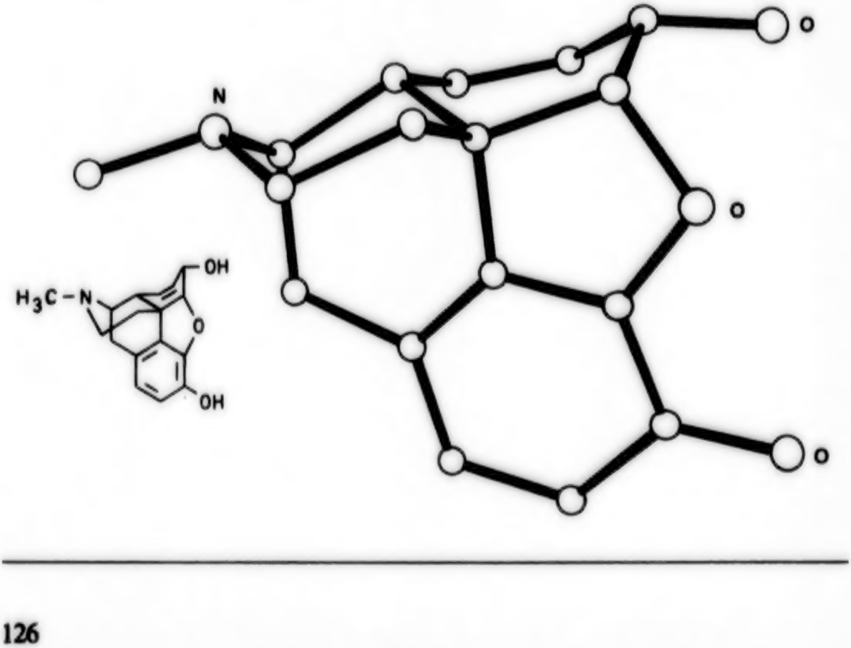
Derivatives of 4–Phenylpiperidines

A large number of morphinomimetics of seemingly unrelated structure have in common either the 4-axial phenyl or 4-equatorial phenylpiperidine fragment.

Pentacyclic structures

The best known structure belonging to this class is the naturally occurring (–) morphine. From Figure 1, which shows the 3–D structure as determined from X-ray crystallographic methods (Gylbert, 1973), it is seen that morphine is a pentacyclic rigid structure and a derivative of 4-axial phenylpiperidine, with the meta-hydroxyphenyl ring in an axial and the N-methyl group in an equatorial orientation relative to the piperidine ring. Its five asymmetric carbon atoms are denoted as 5R, 6S, 9R, 13S and 14R. The morphinomimetic activity of morphine resides solely in the (–) enantiomer (Janssen and Van Der Eycken, 1968). Codeine, azidomorphine, pholcodine, heroin and the antagonists nalorphine and naloxone are all classified as pentacyclics.

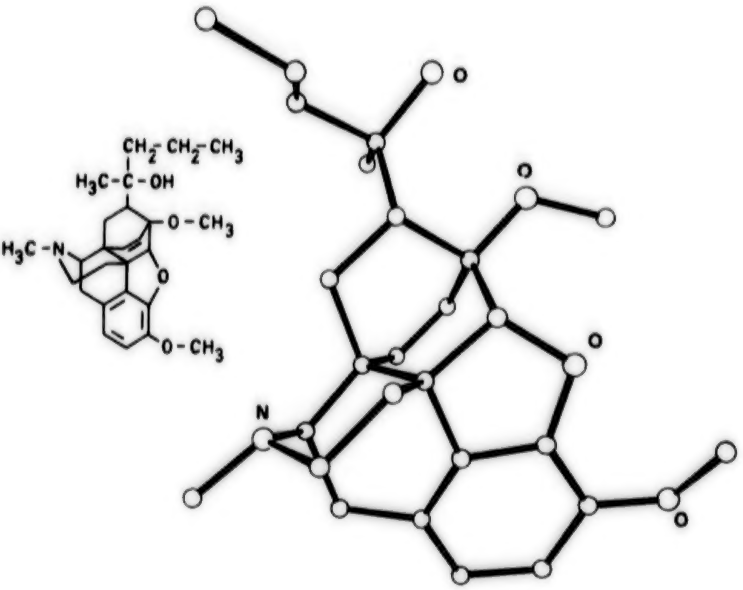
Figure 1
(–) morphine



Hexacyclic structures

Hexacyclic structures derived from thebaine, some of which are several hundred times more potent than morphine, are characterized by a sixth ring system. In Figure 2, which shows the conformation of 19-propylthevinol (Van den Hende and Nelson, 1967), the basic ring skeleton of morphine can easily be seen. The absolute configuration of the hydroxyalkyl group is of major importance for the morphinomimetic activity of this class of compounds.

Figure 2
19-propylthevinol



Tetracyclic structures

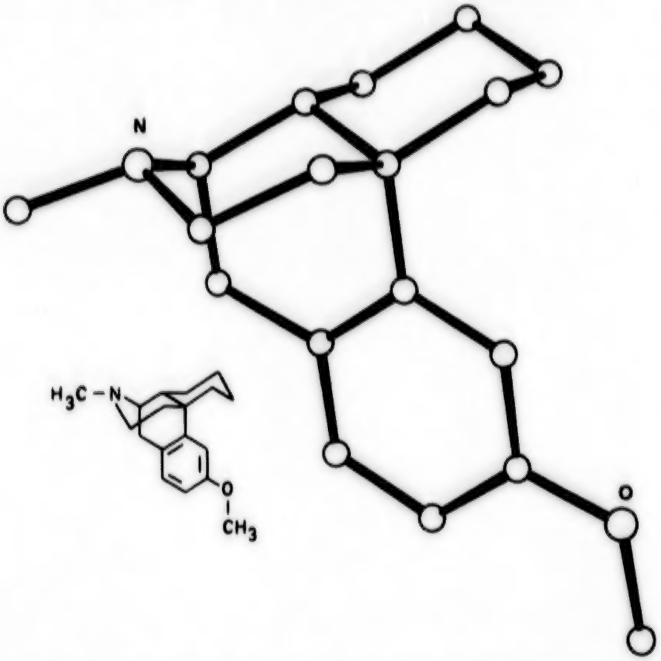
In contrast to the thebaines, which have a more complex structure than morphine, morphinomimetic activity is shown by compounds possessing tetracyclic structures or the so-called morphinans. From the structure of the levo-isomer of dextromethorphan (Gylbert and Carlstrom, 1977) shown in Figure 3, it is clear that upon deletion of the ether oxygen, a tetracyclic structure results, in which part of the morphine is still discernible.

Tricyclic structures

In the last five years or so a great deal of X-ray crystallographic

Figure 3

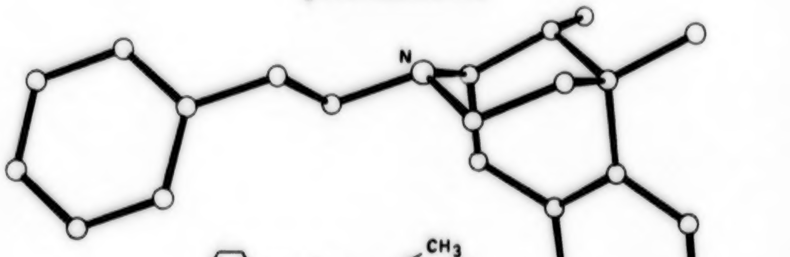
levo-isomer of dextromethorphan



work has been performed on morphinomimetic tricyclics or the benzomorphans. Depending on the nature of the substituent on the nitrogen atom of the piperidine ring, morphinomimetic agonistic and antagonistic effects ensue. In Figure 4 the structure (Gelders *et al.*, 1980) of the potent agonist phenazocine is depicted. Other structures belonging to this

Figure 4

phenazocine



class of compounds include metazocine, dimephen, cyclazocine, pentazocine, ketazocine, and ethylketazocine.

Bicyclic structures

Ever since the synthesis of pethidine (meperidine), the structure (Van Koningsveld, 1970) of which is shown in Figure 5, literally thousands of 4-phenylpiperidine derivatives have been synthesized and tested (Janssen and Van Der Eycken, 1968). As can be seen from Figure 5, the phenyl adopts an equatorial position in the piperidine ring, in contrast to the axial phenyl position of the morphinomimetics thus far discussed. Other compounds belonging to this class of compounds are, for example, the α- and β-prodines and their derivatives, the α- and β-promedols and their derivatives, ketobemidone and phenoperidine.

As a result of the extensive research in the field of substituted 4-phenylpiperidines, a vast body of evidence has accumulated, suggesting that opiate receptors are stereospecific (Portoghese, 1978 and references cited therein).

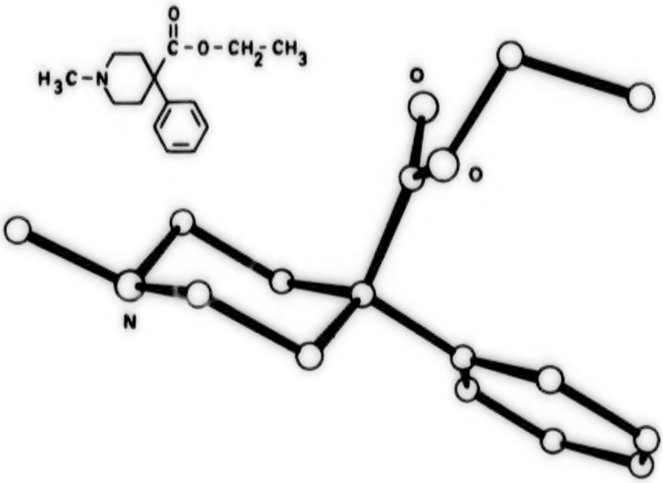


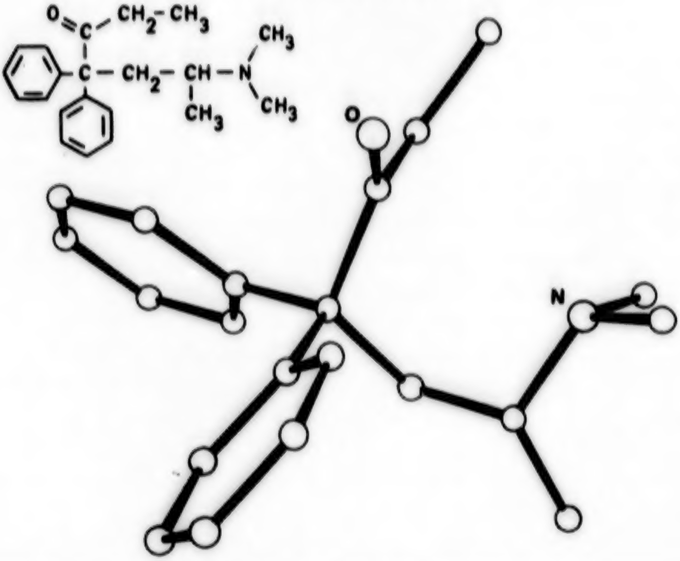
Figure 5
meperidine

3,3-Diphenylpropylamines

The crystal structure conformation (Bürgi *et al.*, 1973) of methadone, the archetype of this class of compounds, is depicted in Figure 6. Other structures in this class possessing morphinomimetic activity equal to or greater than morphine are, for example, isomethadone, dextromoramide, methadol, and acetylmethadol. Long-acting, optically inactive compounds also belonging to this class of compounds include bezitramide and piritramide.

Figure 6

(−) R-methadone

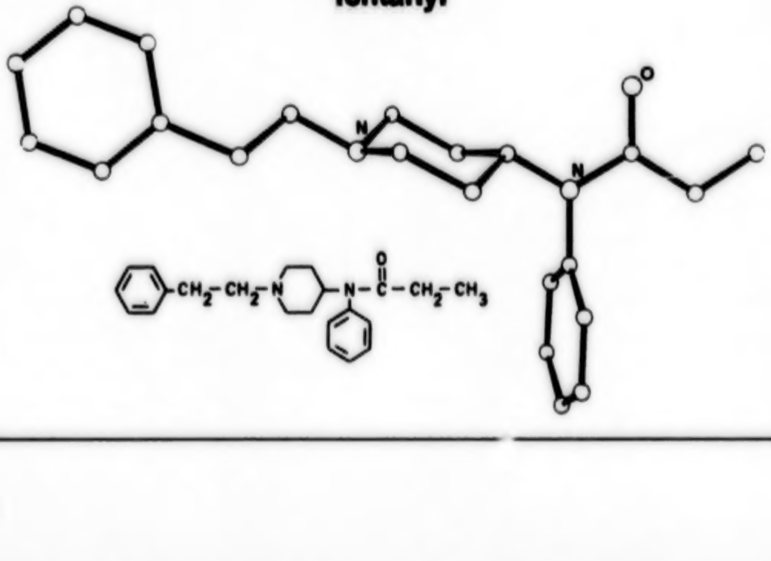


Fentanyl and derivatives

Fentanyl, whose crystal structure conformation (Peeters *et al.*, 1979) appears in Figure 7, and many of its derivatives belong to the most potent class of morphinomimetics known. Depending on the nature of the substituent on the 3- or 4-position of the piperidine ring, derivatives arise exhibiting analgesic potencies several thousand times that of morphine (Van Bever *et al.*, 1974; Van Bever *et al.*, 1976; Van Daele *et al.*,

Figure 7

fentanyl



1976; Janssen and Tollenaere, 1979). In addition to X-ray crystallographic work, theoretical conformational analysis studies have addressed the problem of the receptor-preferred conformation of fentanyl and its derivatives (Tollenaere *et al.*, 1986).

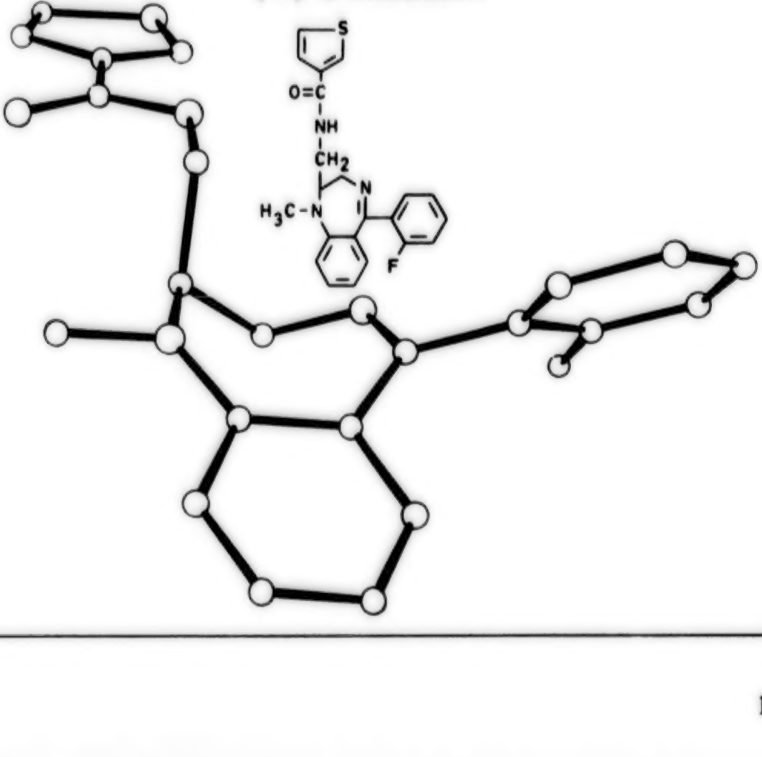
The best known compounds related to fentanyl are carfentanil, lofentanil, alfentanil and sufentanil, the latter having a morphinomimetic activity on the order of 4,000 to 5,000 times that of morphine as well as an unusually high safety margin.

Miscellaneous compounds

The fact that a relatively large number of morphinomimetics having vastly different structures from the ones discussed thus far, defying any reasonable classification, suggests that our knowledge of the opiate-receptor topography is still rudimentary and/or may be taken as evidence for the existence of various subpopulations of the opioid receptor. In fact, compelling evidence from behavioral, pharmacological and biochemical studies indicates the existence of several subpopulations of the opioid receptor (Zukin and Zukin, 1984). In contrast to most morphinomimetics described above, which can be designated as μ-receptor agonists, tifluadom is an example of an effective opioid analgesic with a preference for the opioid κ-receptor. From Figure 8, which shows the crystal structure conformation of tifluadom (Petcher *et al.*, 1985), it is seen that (+)-S-tifluadom is a 1,4-benzodiazepine derivative and consequently is structurally totally unrelated to any of the above compounds.

Figure 8

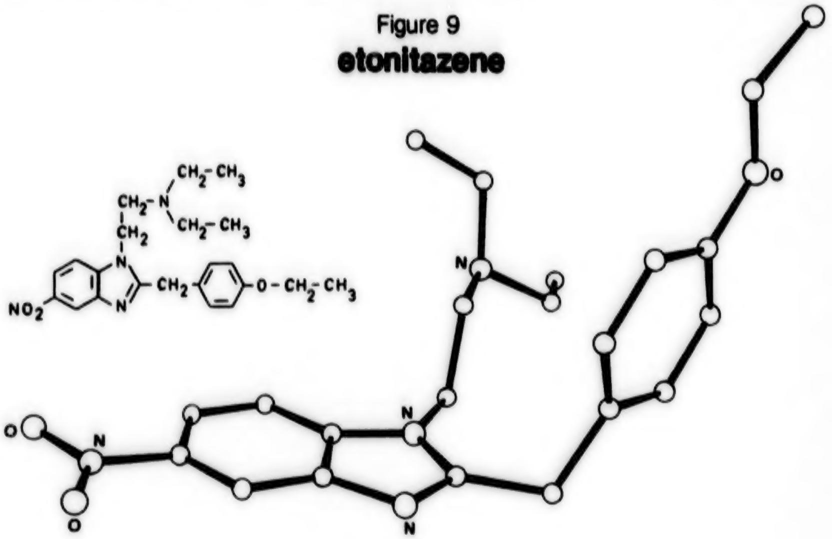
(+)-S-tifluadom



The potent μ-opiate etonitazene, with an analgesic activity of approximately 1,000 times that of morphine, is another example of a structure which has resisted all attempts at classification. As can be seen from the representation of the crystal structure conformation (Humblet, 1978) in Figure 9, etonitazene is a basic nitro-substituted benzimidazo derivative.

Figure 9

etonitazene



Conclusion

Over the last few decades an overwhelmingly large number of synthetic morphinomimetics has been synthesized and tested. A thorough comparison reveals, both topologically and topographically, that a reasonably successful classification of most of the various structures can be made. The fact, however, that a considerable number of very potent analgesic compounds having unexpected structures cannot be assigned to any of the existing structural classes would lead us to expect that new unexpected structures will be encountered in the future.

References

Bürgi, H.B., Dunitz, J.D. and Shefter, E., 6-Dimethylamino-4,4-diphenyl-3-heptanone (methadone), $C_{21}H_{22}NO$, *Crystallogr. Struct. Commun.*, 2: 667–672, 1973.

Gelders, Y.G., De Ranter, C.J. and Kokkes, M., Structural studies of substituted 6,7-benzomorphan compounds. IV (±)-5-ethyl-2′-hydroxy-9,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide (dimephen) and (±)-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (phenazocine) hydrobromide hemihydrate, *Acta Crystallogr,* B36: 1141-1146, 1980.

Gylbert, L., The crystal and molecular structure of morphine hydrochloride trihydrate, *Acta Crystallogr.,* B29: 1630-1635, 1973.

Gylbert, L. and Carlstrom, D., The structure and absolute configuration of (+)-3-methoxy-N-methylmorphinan (dextromethorphan) hydrobromide monohydrate, *Acta Crystallogr.,* B33: 2833-2837, 1977.

Humblet, C., Private communication, 1978.

Janssen, P.A.J. and Van Der Eycken, C.A.M., The chemical anatomy of potent morphine-like analgesics, Burger, A., ed., Marcel Dekker, Inc., New York, pp. 25–60, 1968.

Janssen, P.A.J. and Tollenaere, J.P., Stereochemical anatomy of morphinomimetics in neurochemical mechanisms of opiates and endorphins, Loh, H.H. and Ross, D.H., eds., Raven Press, New York, pp. 103–129, 1979

Peeters, O.M., Blaton, N.M., De Ranter, C.J., Van Herk, A.M. and Goubitz, K., Crystal and molecular structure of N-[1-(2-phenylethyl)-4-piperidinylium]-N-phenylpropanamide (fentanyl) citrate-toluene solvate, *J. Crystallogr. Struct.,* 9: 153-161, 1979.

Petcher, T.J., Widmer, A., Maetzel, U. and Zeugner, H., Structures of tifluadom [5-(2-fluorophenyl)-1-methyl-2-(3-thenoylaminomethyl)-2,3-dihydro-1H-1,4-benzodiazepine]hydrochloride, $C_{22}H_{21}FN_3OS^+$. Cl^-, and of (+)tifluadom p-toluenesulphonate, $C_{22}H_{21}FN_3OS^+$. $C_7H_7O_3\ S^-$, and the absolute configuration of the latter, *Acta Crystallogr.,* C41: 909–912, 1985.

Portoghese, P.S., Stereoisomeric ligands as opioid receptor probes, *Acc. Chem. Res.,* 11: 21–29, 1978.

Tollenaere, J.P., Moereels, H. and Raymaekers, L.A., Atlas of the three-dimensional structure of drugs, Elsevier/North-Holland Biomedical Press, Amsterdam, New York, Oxford, 1979.

Tollenaere, J.P., Moereels, H. and Van Loon, M., On conformation analysis, molecular graphics, fentanyl and its derivatives, *Prog. Drug Res.,* 30: 91–126, 1986.

Van Bever, W.F.M., Niemegeers, C.J.E. and Janssen, P.A.J., Synthetic analgesics. Synthesis and pharmacology of the diastereoisomers of N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide and N-[3-methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide, *J. Med. Chem.,* 17: 1047-1051, 1974.

Van Bever, W.F.M., Niemegeers, C.J.E., Schellekens, K.H.L. and Janssen, P.A.J., N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin, *Arzneim. Forsch.,* 26: 1548-1551, 1976.

Van Daele, P.G.H., De Bruyn, M.F.L., Boey, J.M., Sanczuk, S., Agten, J.T.M. and Janssen, P.A.J., Synthetic analgesics: N-(1-[2-arylethyl]-

4-substituted 4-piperidinyl)N-arylalkanamides, *Arzneim. Forsch.*, 26: 1521-1531, 1976.

Van den Hende, J.H. and Nelson, N.R., The crystal and molecular structure of 7α-(1-(R)-hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine hydrobromide (19-propylthevinol hydrobromide), *J. Am. Chem. Soc.*, 89: 2901–2905, 1967.

Zukin, R.S. and Zukin, R., The case for multiple opiate receptors, *Trends Neurosci.*, 7: 160–164, 1984.

Preclinical Pharmacology of Drug Abuse

K. Kelemen, M.D., D.Sc.

"As far back as recorded history, every society has used drugs that produce effects on mood, thought, and feeling. Moreover, there were always a few individuals who digressed from custom with respect to the time, the amount, and the situation in which these drugs were to be used. Thus both the nonmedical use of drugs and the problem of drug abuse are as old as civilization itself" (Jaffe, 1985).

Drug dependence, however, is not confined to humans and many major aspects of drug abuse can be observed and studied in laboratory mammals. Moreover, all known drugs with abuse liability in man evoke characteristic pharmacological effects in animals and several relatively simple tests are available to study these effects in the laboratory.

Tolerance and physical dependence are most frequently but not necessarily associated with the development of compulsive drug abuse.

Tolerance is a reduced effectivity after repeated administration of the drug requiring increasingly larger doses to obtain the same effect. Tolerance does not develop uniformly to all the actions of a drug. There may be complete tolerance to some actions, while responses to others are more or less unaltered. For example, in the case of *opioids*, considerable tolerance develops to the analgesic, euphorigenic and other central nervous system (CNS) depressant effects (including respiratory depression which is responsible for death from narcotic overdose) while no tolerance develops to the miotic and constipating effects. Medical problems arise from the prevalence and intensification of those effects to which no tolerance has developed. In the case of alcohol, tolerance to toxic effects may not develop in parallel with tolerance to CNS depression. Thus the consumption of more alcohol in order to obtain the desired effects may increase the risk of drug-induced organ damage. With amphetamines, a significant degree of tolerance to the euphorigenic, anorectic, hyperthermic and lethal effects may be accompanied even by an increased sensitivity to some toxic action (toxic psychosis). A high degree of tolerance to the behavioral effects of lysergide (LSD) develops after three or four daily doses but tolerance to the cardiovascular effects is less pronounced.

Physical dependence is an altered physiological state produced by the repeated administration of a drug. In this state the continued administration of the drug is necessary to prevent the appearance of a characteristic group of symptoms, the *withdrawal* or *abstinence syndrome*. Physical dependence develops during the chronic administration of opioids, hypnotics, alcohol, amphetamines, cannabinoids and nicotine. Withdrawal symptoms are usually *rebound effects*. General depressants elevate the seizure threshold and spontaneous seizures appear during withdrawal. Amphetamines alleviate fatigue, suppress appetite and elevate mood while amphetamine withdrawal is characterized by lack of energy, hyperphagia and depression. Physical dependence may develop rapidly. Withdrawal symptoms can be induced by naloxone, an opioid antagonist, even after a single injection of morphine or heroin in the mouse (Wiley and Downs, 1979).

Withdrawal signs include tremor, teeth chattering, wet dog shakes, tachycardia, hyperventilation and diarrhea. After three days of chronic exposure to ethanol, mice developed marked physical dependence, with spontaneous seizures upon abrupt withdrawal (Tabakoff and Hoffman, 1983). This rapid development of physical dependence may explain the fact that a human taking a short-acting drug to induce euphoria or reduce tensions will soon experience dysphoria and exacerbation of tensions (rebound effects) as the drug is eliminated from the body. This prompts him to take the drug again and the alleviation of the withdrawal symptoms reinforces the drug-using behavior.

Withdrawal symptoms and their relief can be conditioned to environmental stimuli both in animals and humans. This may be one of the reasons why taking placebos (an inert pill or injection of saline) can, under appropriate conditions, evoke the well-being, and even the relief of withdrawal symptoms, previously produced by the active drug (Wikler, 1980; Donegan *et al.*, 1983).

Cross-tolerance and *cross-dependence* may develop within groups of structurally or pharmacologically related drugs. Thus, individuals (humans and animals alike) may display a certain degree of insensitivity to drugs never experienced before and some drugs can substitute for other ones in relieving withdrawal symptoms.

Tolerance and physical dependence are, however, not necessarily linked to compulsive drug use. They may develop after the chronic administration of drugs without any abuse liability, like anticholinergics, chlorpromazine or imipramine.

The most important factor of drug dependence, as a medical and social problem, is *compulsive drug abuse*, a craving for the drug. Man's passion to take drugs is shared with other mammals. Laboratory animals are ready to self-administer the majority of drugs used compulsively by man. If these drugs are accessible, animals behave very much like human abusers, suggesting that beside social and psychological factors, the reinforcing properties of the drugs themselves play a very important part in drug abuse. Some drugs, like chlorpromazine, seem to have aversive properties and animals try to avoid them at the same time when they are ready to press a lever several thousand times to get a single injection of cocaine. They even self-administer enormously high daily doses which produce severe toxic effects and kill the animals (Johanson and Schuster, 1981). There are characteristic "reward" areas in the rat's brain which are, through implanted electrodes, passionately self-stimulated by the animals, by means of lever pressing. Both CNS stimulant sympathomimetics, like amphetamines and cocaine, and opioids, like morphine, lower the intensity of electric current required to produce "rewarding" effects in these brain areas (Kornetsky and Esposito, 1981).

Drugs with Abuse Liability

1. *Opioids*

A group comprising the drugs derived from opium (morphine and codeine), their semisynthetic congeners, the many totally synthetic entities with morphine-like actions and the endogenous opioid peptides.

2. *CNS sympathomimetics*

Amphetamines, cocaine, cathinone.

3. *Hallucinogens* (psychedelics, psychotomimetics)

LSD, psilocybin, mescaline.

4. *Arylcyclohexylamines*

Phencyclidine (PCP).

5. *General CNS depressants*

Barbiturates, benzodiazepines.

6. *Alcohol.*

7. *Nicotine and tobacco.*

8. *Cannabinoids* (marihuana).

9. *Inhalants.*

10. *Anesthetic gases and solvents, glue*

For the present topic, the first four items are of primary interest. Like other such groupings, this is a highly imperfect classification. Very important drugs, like dimethoxyamphetamine (DMA), 2,5-dimethoxy-4-methylamphetamine (DOM), 3,4-methylenedioxyamphetamine (MDA), 5-methoxy-3,4-methylenedioxyamphetamine (MMDA) do not find their proper place as they may be equally classified as CNS sympathomimetics (group 2) or hallucinogens (group 3). PCP which is, due to its structure and pharmacological actions, an independent item, has very pronounced psychedelic properties and has a quite peculiar relationship to a certain opioid receptor.

Opioids

This group comprises a great variety of compounds which share some morphine-like (or morphine antagonistic) properties. Many semisynthetic and synthetic derivatives of the morphine molecule, other synthetic analgesics like phenylpiperidines (meperidine and congeners, fentanyls included), diphenylheptanes (pentazocine and congeners) together with some naturally-occurring peptides (the enkephalins, the endorphins and the dynorphins) all belong to this group. This structural heterogeneity determines the variations in the pharmacological effects of these drugs which, beside some relevant common properties, display very important individual differences.

The discovery of the endogenous opioid peptides, i.e., the "morphines" produced in our body which as neurotransmitters and neuro-hormones seem to play a crucial role in fundamental physiological functions, has given rise to much speculation as to why opioids of plant and synthetic origin can be so important for human beings. Beta-endorphin levels are increased in the cerebrospinal fluid (CSF) after stimulation to produce pain relief, after acupuncture but also in heroin addiction. Levels of metenkephalin in human CSF are reduced during migraine attacks and in heroin addicts and are elevated after electroacupuncture for relief of withdrawal symptoms in heroin addicts (Kuhar and Pasternak, 1984). But enzymatic activity and poor passage of these peptides across the blood-brain-barrier make them unlikely candidates for drugs of abuse or for clinical use.

It is now generally accepted that the heterogeneity of opioids is related to the existence of different receptors, specific binding sites in the brain and other organs. Four major receptors, identified as mu, kappa, sigma and delta with various subtypes, are distinguished by the different compounds which can bind with different affinities and exert agonistic, antagonistic or partial agonistic effects.

The relationship of some opioid drugs to the different receptor types is shown in Table 1.

Table 1

Prototypes of Agonist, Antagonist and Mixed Agonist-Antagonist Compounds at Opioid Receptors

	Receptor types		
Compound	**Mu**	**Kappa**	**Sigma**
Morphine	Ag	Ag	—
Naloxone	Ant	Ant	pAnt
Pentazocine	Ant	Ag	Ag
Butorphanol	—	Ag	Ag
Nalorphine	Ant	pAg	Ag
Buprenorphine	pAg	—	—
N-allyl-normetazocine	Ant	—	Ag

The mu receptor is thought to mediate supraspinal analgesia, respiratory depression, euphoria, and physical dependence; the kappa receptor mediates spinal analgesia, miosis, and sedation; the sigma receptor mediates dysphoria, hallucinations and respiratory and vasomotor stimulation. The classification of the delta receptors has been mainly necessitated by the different effects of opioid peptides and drugs which inhibit contractions of the isolated guinea pig ileum and mouse vas deferens.

It would be tempting to focus our attention on drugs with an agonistic effect on mu receptors, responsible for euphoria and physical dependence, as indeed, morphine, heroin and fentanyl are all potent mu receptor agonists. This rather simplified view proved, however, erroneous. For instance, pentazocine, an opioid of mixed action and a mu receptor antagonist, which does not prevent but precipitates a morphine withdrawal syndrome, proved to be addicting by itself and became popular for intravenous abuse in combination with tripelennamine, an antihistamine. Phencyclidine (PCP), a hallucinogen, seems to be related to the sigma receptor which is responsible for the dysphoria and hallucinations caused by some opioids.

The most important pharmacological effects of morphine are summarized in Table 2. Mu agonists share the majority of these properties with morphine but other opioids, as shown above, may differ considerably.

Table 2

Pharmacological Effects of Morphine

Central nervous system

- Analgesia
- Drowsiness
- Euphoria
- Nausea, vomiting
- Respiratory depression
- Hypothermia
- Hormonal disturbances
- EEG alterations
- Changes of the pupil (miosis followed by mydriasis)
- Excitation (pronounced in certain species)

Other

- Cardiovascular changes (vasodilation)
- Increased smooth muscle tone (stomach, bowels, biliary tract, urinary tract)
- Decreased gastrointestinal motility

Several laboratory tests are available to reveal and analyze the effects of opioids. They are also suitable to identify unknown compounds as opioids and to predict, with more or less reliability, their potential abuse liability in man. The majority of these tests are simple and can be carried out in the rat and mouse, i.e., in relatively cheap laboratory animals. Some tests for a deeper analysis necessitate the use of monkeys, and others (such as receptor binding assays) require sophisticated laboratory equipment (Wood, 1984).

Some of the most important laboratory tests are summarized in Table 3. By the use of some quick analgesia and dependence potential tests a superficial profile of a potential opioid drug can be obtained in a relatively short time.

Amphetamines

Amphetamine is a well-defined chemical compund (beta-phenylisopropylamine) which has powerful CNS stimulant and hypertensive ac-

Table 3

Some Experimental Models for Testing of Opioids in Laboratory Animals

ANALGESIA TESTING

- **Heat stimuli**
  - Tail flick (rodents)
  - CO_2 laser (rodents)
  - Hot plate (rodents)
- **Electrical stimuli**
  - Stimulation of the tail (rodents)
  - Stimulation of the dental pulp (dog)
  - Shock titration (rat or monkey)
- **Chemical stimuli**
  - Writhing assay (rodents)
  - Hyperesthesia (rodents)

DEPENDENCE POTENTIAL

- Self-administration (rat or monkey)
- Primary dependence (rodents and monkey)
- Precipitated withdrawal (rodents and monkey)
- Cross-tolerance (rodents and monkey)

ISOLATED ORGAN TECHNIQUES (Neurotransmitter release inhib.)

- Guinea pig ileum
- Mouse vas deferens

BIOCHEMICAL TECHNIQUES

- Receptor binding assays

Table 4

Pharmacological Effects of Amphetamines

- Wakefulness, alertness
- EEG activation
- Increased psychological and physiological performance followed by fatigue
- Decrease of appetite
- Increase of oxygen consumption
- Hyperthermia
- Blood pressure rise
- Cardiac arrhythmia
- Convulsions, coma, cerebral hemorrhage

tions. Its most important pharmacological effects are summarized in Table 4. There are many congeners with structural and pharmacological similarities which are usually called *amphetamines*. Dextroamphetamine, methamphetamine, phenmetrazine, methylphenidate and diethylpropion (amfepramone) differ only quantitatively (in the doses required to evoke the characteristic effects) from amphetamine. Some congeners, like fenfluramine or phenylpropanolamine, however, do not evoke amphetamine-like subjective effects and are not self-administered by laboratory animals (Griffiths *et al.*, 1978). Some compounds, chemically derived from amphetamine, possess LSD-like hallucinogenic properties (DOM, DMA) or are mixed stimulants/hallucinogenics, like MDA or MMDA (Martin *et al.*, 1971). According to the description of *cocaine* addicts, the euphoric effect of cocaine is almost indistinguishable from that of amphetamine (Fischman and Schuster, 1982). The toxic syndrome caused by cocaine is also practically identical with that evoked by amphetamine and experimental animals exhibit identical patterns of self-administration. *Cathinone*, the active factor in the leaves of *Catha edulis* also has amphetamine-like properties.

If amphetamines or cocaine are continually accessible, laboratory animals get quickly addicted to them and follow a characteristic self-administration pattern. They lose weight, get prone to self-mutilation and usually die within two weeks. Given a choice between cocaine and food, monkeys consistently select cocaine (Aigner and Balster, 1978).

The typical effects of amphetamine can be demonstrated in a great variety of laboratory tests, some of which are listed in Table 5. A marked increase in the motor activity of mice or rats and the antagonism of the depressant effect of neuroleptics (e.g. chlorpromazine) on motility, which can easily be checked by simple devices, may suggest an amphetamine-like property of an unknown substance.

Table 5

Some Experimental Models for Testing of Amphetamines in Laboratory Animals

Increase of spontaneous motor activity
Activation in different behavioral tests
Improved acquisition and retention of learning
Intensification of fighting behavior
Antagonism of neuroleptic effects
Increase of oxygen consumption
Increase of body temperature
Self-administration

Hallucinogens

Hallucinogens are drugs which cause alterations of mood and thinking (illusions, hallucinations, delusions, etc.) similar to those occurring in endogenous psychoses. These phenomena are typical subjective effects in humans. Those who experience these feelings can speak about them to fellow-people by means of their language, a way of communication not shared with our experimental animals. There is no reason to suppose that rats or dogs have no subjective world of their own and even their own hallucinations, but these phenomena are beyond the reach of the usual laboratory studies. Thus, in detecting and analyzing hallucinogenic drugs in the experimental animals we are confined to some vegetative effects which are mere accompanying symptoms in the complex action of these drugs. There are some common effects of the known hallucinogens (LSD, mescaline, psilocybin, etc.) which are manifested mainly in their influence on the sympathetic nervous system. In most of the laboratory animals pupillary dilation, increase in blood pressure, tachycardia, hyperreflexia, tremor, nausea, piloerection, muscular weakness and changes in body temperature are observed. These are rather non-specific signs, also produced by many other drugs. This is the reason why so many diverse tests have been described for the study of these compounds. Otis *et al.*, (1978) have identified 52 test procedures from the literature as promising. These were culled to 12 on the basis of a set of criteria that emphasized reliability and simplicity of execution. Finally, from the procedures selected for intensive laboratory investigations, only three proved sufficiently discriminatory and reliable. They claim that the use of three simple tests:

1) rat body temperature
2) rabbit body temperature and
3) photocell activity (spontaneous motor activity) of the rat is sufficient to classify unknown compounds into one of three drug classes—Hallucinogen, Stimulant or Other.

Compounds which increase all the three measured parameters are stimulants (amphetamine-like), those which increase only rabbit body temperature but decrease both body temperature and spontaneous motor activity of the rat are hallucinogens (LSD–like) and any other combination excludes the drug from these two categories. This battery of tests, in the hands of the authors, has correctly identified all 28 compounds submitted for double blind evaluation as belonging to one of the above three classes.

Arylcyclohexylamines

Phencyclidine (PCP) represents an independent entity. It had been used clinically as a general anesthetic for a time, but due to its hallucinogenic effect, it was quickly withdrawn from the market for human application. It has CNS-stimulant, CNS-depressant, hallucinogenic and analgesic actions. The name *dissociative anesthetic* was given to this drug because under its influence surgical operations were performed without pain and with complete amnesia to intervention while the patient had some, although distorted, contact with the external world during anesthesia. In contrast to LSD, which is not self-administered by monkeys, self-injection of PCP seems to be "rewarding" to these animals (Aniline and Pitts, 1982). As mentioned above, PCP is likely to act on the sigma opioid receptor, considered responsible for the dysphoric and hallucinogenic effects of some opioid drugs. In the battery of tests recommended by Otis *et al.*, (1978), PCP was judged, under double-blind conditions, to be a hallucinogen but it was difficult to differentiate it from stimulants.

The "modified jumping test": a method for quick orientation

The modfied jumping test has been described by Knoll (1973) as a method for quick orientation in drug research. Rats are placed onto a metal plate of 45°C under a glass cylinder open at the top and the bottom. This mild heat does not evoke any abrupt escape reaction but animals get slowly overheated and almost every rat is capable of discovering, without any previous learning, the only way of escape and after a shorter or longer latency they jump to the top of the cylinder. Rats pretreated with effective doses of psychotropic agents lose this capacity of adaptation to the new environment and, if not removed from the plate, die of hyperthermia. Different classes of psychotropic drugs have the same effect (Table 6). But a reliable differentiation is possible by the use of specific pharmacological antagonists. As shown in Table 6, the opioid morphine, the neuroleptic chlorpromazine, the hypnotic phenobarbital and the hallucinogen LSD equally prevent the adaptive reaction but the opioid antagonist naloxone counteracts the effect of morphine (and only that of morphine) and pentylenetetrazol is effective only against the hypnotic drug. Amphetamine antagonizes the effects of both neuroleptics

Table 6

Differentiation of Psychotropic Drugs by Specific Antagonists in the Modified Jumping Test

Test drugs	No antag	Antagonist Naloxone	 Amphetamine	 Pentylentetrazole	 Caffeine
Opioids					
like morphine	0	+	0	0	0
Neuroleptics					
like chlorpromazine	0	0	+	0	0
Sedatohypnotics					
like phenobarbital	0	0	+	+	+/−
Hallucinogens					
like LSD	0	0	+/−	0	0

0 = no jumping, animals die of hyperthermia if not removed
+ = majority of animals jump with a normal reaction time
+/− = a small percentage of the animals jump

and sedative-hypnotics but they can be easily differentiated by the lack of effect of pentylenetetrazol against neuroleptics. LSD-like drugs are characterized, in this test, by the absence of a specific antagonist.

Amphetamine behaves in a somewhat different manner. As shown by Table 7, relatively low doses of amphetamine improve the adaptive reaction (animals jump with a shorter latency than the controls) but higher doses which cause incoordination, hinder the escape. This effect of high anphetamine doses can be counteracted by alpha-methyltyrosine or para-chlorophenylalanine—drugs which interfere in the brain with the synthesis of neurotransmitters necessary for the action of amphetamines.

Table 7

Identification of the Amphetamine-Type Stimulant Effect by the Modified Jumping Test

		Antagonist		
Test Drug	**Dose mg/kg**	**No antag.**	**alpha-methyl-tyrosine**	**parachlorphenyl alanine**
Amphetamine	2.0	+ + +		
Amphetamine	10.0	0	+	+

0 = no jumping, animals die of hyperthermia if not removed
+ = majority of animals jump with a normal reaction time
+ + + = reaction time of jumping is significantly shortened

Conclusion

Drugs with abuse liability in man have characteristic effects in experimental animals. Simple laboratory tests can be helpful in the first orientation about the type of action of an unknown substance.

References

Aigner, T.G. and Balster, R.L., Choice behavior in rhesus monkeys: cocaine versus food. *Science,* 201, 534–535, 1978.

Aniline, O. and Pitts, F.N., Phencyclidine (PCP): a review and perspectives. *CRC Crit. Rev. Toxicol.,* 10, 145–177, 1982.

Donegan, N.H., Rodin, J., O'Brien, C.P.: A learning-theory approach to commonalities. In: *Commonalities in Substance Abuse and Habitual Behavior.* Lexington Books, Lexington, 1983, pp. 111–156.

Fischman, M.W. and Schuster, C.R., Cocaine self-administration in humans. *Fed. Proc.,* 41: 241–246.

Griffiths, R.R., Brady, J.V., Snell, J.D., Progressive-ratio performance maintained by drug infusions. *Psychopharmacology,* 56, 5–13, 1978.

Jaffe, J.H., Drug Addiction and Drug Abuse. In: Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 7th Edition, Macmillan, New York, 1985.

Johanson, C.E. and Schuster, C.R., Animal models in drug self-administration. In: *Advances in Substance Abuse; Behavioral and Biological Research*, Vol. II (Mello, N.K., ed.) JAI Press Inc. Greenwich, Conn., 1981, pp. 219–297.

Knoll, J., Modulation of learning and retention by amphetamines. In: *Pharmacology and the Future Man*, Vol. 4, pp. 55–68, Karger, Basel, 1973.

Kornetsky, C. and Esposito, R.U., Reward and detection thresholds for brain stimulation. *Brain. Res.* 496–500, 1981.

Kuhar, M.J. and Pasternak, G.W. (Editors), *Analgesics: Neurochemical, Behavioral, and Clinical Perspectives*, Raven Press, New York, 1984.

Martin, W.R., Sloan, J.W., Sapira, J.D., and Jasinski, D.R., Physiologic, subjective, and behavioral effects of amphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin. Pharmacol. Ther.*, 12, 245–258, 1971.

Otis, L.S., Pryor, G.T., and Marquis, W.J., Preclinical identification of hallucinogenic compounds. In: Stilman, R.C. and Willette, R.E. (Editors) *The Psychopharmacology of Hallucinogens*, Pergamon Press, New York, pp. 126–149, 1978.

Tabakoff, B. and Hoffman, P.L., Neurochemical aspects of tolerance to and physical dependence on alcohol. In: *Biology of Alcoholism*, Vol. 7 (Kissin B. and Begleiter H., eds.) Plenum Press, New York, 1983, pp. 199–252.

Wikler, A., *Opioid Dependence: Mechanisms and Treatment.* Plenum Press, New York, 1977.

Wiley, J.N., and Downs, D.A., Naloxone-precipitated jumping in mice pretreated with acute injections of opioids. *Life Sci.*, 25: 797–802, 1979.

Wood, L., Animal models in analgesic testing. In: *Analgesics: Neurochemical, Behavioral, and Clinical Perspectives* (Kuhar, M.J. and Pasternak, G.W., Editors), Raven Press, New York, 1984.

BLANK PAGE

Clinical Pharmacology and Designer Drugs

Jordi Camí, M.D.

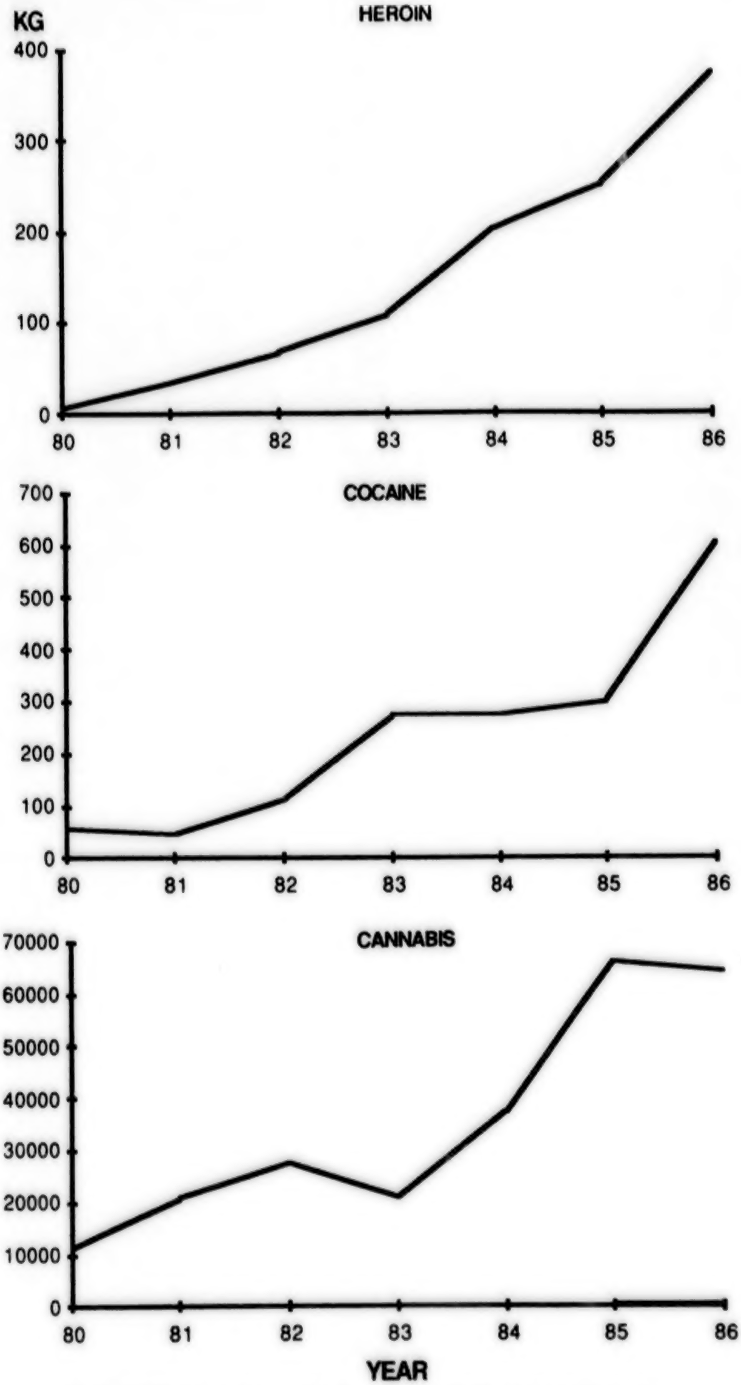
Drug Consumption in Spain

At present the three illicit drugs causing major concern in Spain are *Cannabis*, in the form of hashish, heroin and cocaine. Figure 1 shows the evolution of confiscations made by the police in the last seven years with respect to the aforementioned drugs (Parlement Européen, 1986). After having suffered an extensive epidemic of traffic in and consumption of heroin—80,000 to 125,000 heroin abusers in the total Spanish population of 34 million (Navarro *et al.*, 1985), Spain is now faced with great expansion of cocaine consumption. Figure 2 illustrates the increasing number of patients admitted to the emergency room of our hospital during recent months due to withdrawal syndrome, overdose or toxic problems related to cocaine abuse (Camí *et al.*, 1987b). A major proportion of these cocaine-related problems comes from its intranasal use. With respect to designer drugs our direct experience is limited. We are not aware of the use of analogues of fentanyl or phencyclidine in Spain. Only small amounts of MDMA have been confiscated during this and last summers in the tourist area of the island of Ibiza. Up to the present time, no one has been convicted in Spanish court because of MDMA or MDA traffic.

Parallel Between Designer Drugs and "Me-Too" Drugs

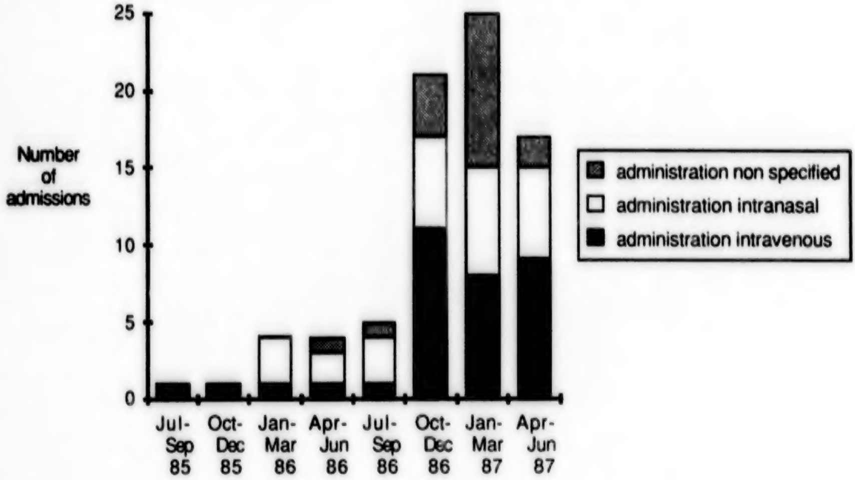
During the last decades, many discrete chemical variants of successful and well-established drugs have been commercialized. From 30 to 50 new chemical entities are introduced annually into the worldwide market; in 1986, 47 new chemical entities were introduced and 34 of them were congeners, popularly called "me-too" drugs (World Pharmaceutical News, 1987). The main purposes of these chemical modification are to enhance potency, to alter pharmacokinetic properties and/or highlight a specific activity. Chemical strategies used to develop su analogues for therapeutic purposes are the same used by clandestine chemists who synthesize designer drugs. The assessment of the real advantages of analogues over the parent compounds is not free of methodological difficulties and is very expensive too. For instance, serious comparative efficacy studies require large samples of patients which are not always available with the resources of some pharmaceutical companies. Frequently, analogues do not offer measurable advantages. But if a

Figure 1



Confiscations made by the Spanish police in the past years.

Figure 2



Quarterly mean of cocaine-related emergencies in Hospital del Mar, Barcelona.

congener presents a real advantage, why do the "parent" drugs remain on the market? (Garattini and Tognoni, 1985). Despite substantial therapeutic advantages presented by some congeners, the general consensus points towards an excessive and unnecessary offering of drugs on the market. The following two cases show the parallelism between "me-too" compounds and designer drugs, and are particular examples of the development of analogues of substances causing dependence with therapeutic purposes.

In the group of benzodiazepines, 25 "me-too" drugs are present on the Spanish market. On the basis of their clinical use, rate of absorption, activity of metabolites, and half-life, they could be divided into two or three groups; thus, all therapeutic requirements attributed to these substances could be covered by only three or four agents (Camí, 1987a). A second example is the use of new potent opioid agonists. The main clinical application of fentanyl is as a supplement to general anesthesia with nitrous oxide; high doses of fentanyl are also used as the sole anesthetic for patients undergoing cardiac surgery. Alfentanil and sufentanil are newer fentanyl derivatives more potent than fentanyl and having a very short elimination half-life. This is a particular advantage during short operations and for day-care surgery (Bovill, 1987). However, such derivatives have pharmacological properties very close to those of alpha-methylfentanyl, 3-methylfentanyl or para-fluorofentanyl, which are analogues synthesized clandestinely. The continuous search for new fentanyl analogues for future commercialization may constitute a therapeutic priority.

Clinical Pharmacology and Dependence Potential

Clinical pharmacology should have a more important role in the controlled evaluation of effects and therapeutic possibilities of drugs of abuse, as well as in the extension of programs of clinical drug abuse liability testing.

In the last decades, standardized and validated clinical testing procedures for studying the abuse liability of psychotropic substances in human subjects have been developed. These methods measure subjective effects of drugs, reinforcing effects, and production of physiological dependence assessed by symptoms of withdrawal which follow abrupt termination of a chronically administered substance (Jasinski *et al.*, 1984). Current methods of drug self-administration are to evaluate dependence potential (liability), to determine what types of pharmacological and environmental manipulations decrease drug-taking behavior and to serve as a means of investigating the pharmacological and behavioral mechanism underlying drug dependence (Johanson *et al.*, 1987).

Subjective Effects as Determinants of Reinforcing Properties

Although the classes of drugs of abuse can be differentiated on the basis of their spectrum of subjective effects, certain effects in common produced by all such drugs appear as determinants of their abuse. Subjective effects would be more important than physiological dependence, or in other words, physiological dependence would be a property neither necessary nor sufficient for maintaining drug-seeking behavior. The abuse seems to be maintained by the reinforcing properties of the drug which are not associated with the presence or absence of physiological dependence, but which are related to distinctive subjective effects. We need a great deal more information on how individuals differ in their subjective responses to drugs.

We are going to present some observations made in our laboratory of clinical experimentation, where since 1981 we performed pharmacodynamic and pharmacokinetic studies on psychoactive substances. In trials of single dose effects, the drug tested is not the only determinant of the pharmacological effects. The response is influenced by the prejudices of the subject concerning the effects of the particular drug, his/her expectation of what will happen according to environmental conditions, and instructions received from the investigators. The balanced placebo design model permits a separate evaluation of the pharmacological effects mediated by the subject's expectations (Marlatt and Rohsenow, 1980). The defining characteristic of the traditional double-blind method is that neither the investigator nor the subject is aware of the true nature of the substance administered (Table 1). In the balanced placebo design, whereas the double-blind strategy of the trial is maintained, and after neutral instructions concerning the drug's effects are given, the expectation

Table 1

Subject Allocation According to Trial Design

Classic Double Blind Assay

Placebo or Control Drug	Test Drug
n subjects	n subjects

Balanced Placebo Design

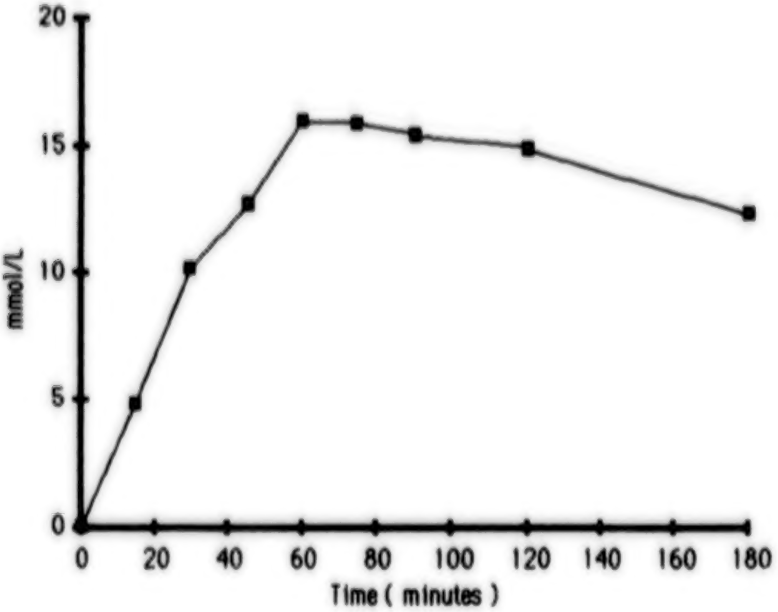
	Placebo	Test Drug
Positive Expectancy	n subjects	n subjects
Negative Expectancy	n subjects	n subjects

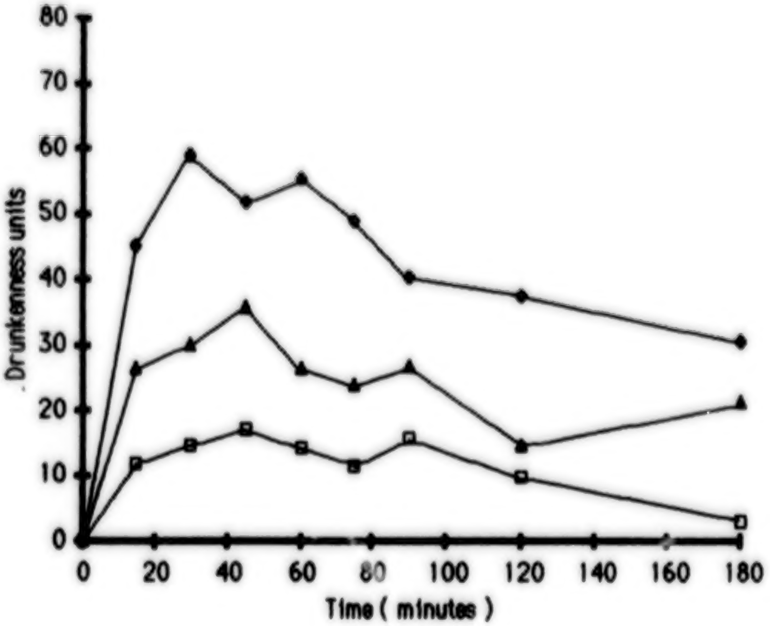
factor is introduced. Immediately before the experiment half of the subjects who are truly given active medication are told that they will receive placebo and vice versa; on the other hand, half of the subjects who will actually receive placebo are told that they will receive active medication and vice versa. Using low doses of alcohol and hashish as the target drugs in paid student volunteers, we achieved a percentage of deception of 94% (no. = 48), and 88% (no. = 48) respectively (Camí *et al.*, 1987c). Under these conditions and when low doses are used, data on self-evaluation of subjective effects is susceptible to multiple interpretations.

In a balanced placebo study using single low doses of alcohol, subjects were invited to carry out a self-evaluation of their drunkenness on a visual analog scale, whereas blood samples were drawn simultaneously for blood alcohol concentrations (Guerra *et al.*, 1986). Figure 3 shows the mean values obtained in the experiment in which doses of alcohol were 0.8 g/kg (six subjects in each group of study). The highest drunkenness score was found in the group of the subjects who were aware of alcohol consumption before the experiment, whereas results of those deceived were very similar to the results seen in the placebo group.

The possibility of manipulating the subjective effects of low alcohol doses in experienced subjects can be also applied in the case of hashish. In a psychopharmacological study on the interaction of hashish and alcohol using a balanced placebo design, 96 young students were selected in order to fulfill the 16 requisite conditions for differentiating groups with false or true expectations from school or hashish consumption, or both (Camí *et al.*, 1987c). Using the same visual analog scale, the time courses

Figure 3





Time-course of blood alcohol concentrations (upper) and self-evaluation of drunkenness (bottom) following oral administration of 0.8 g/Kg of alcohol.

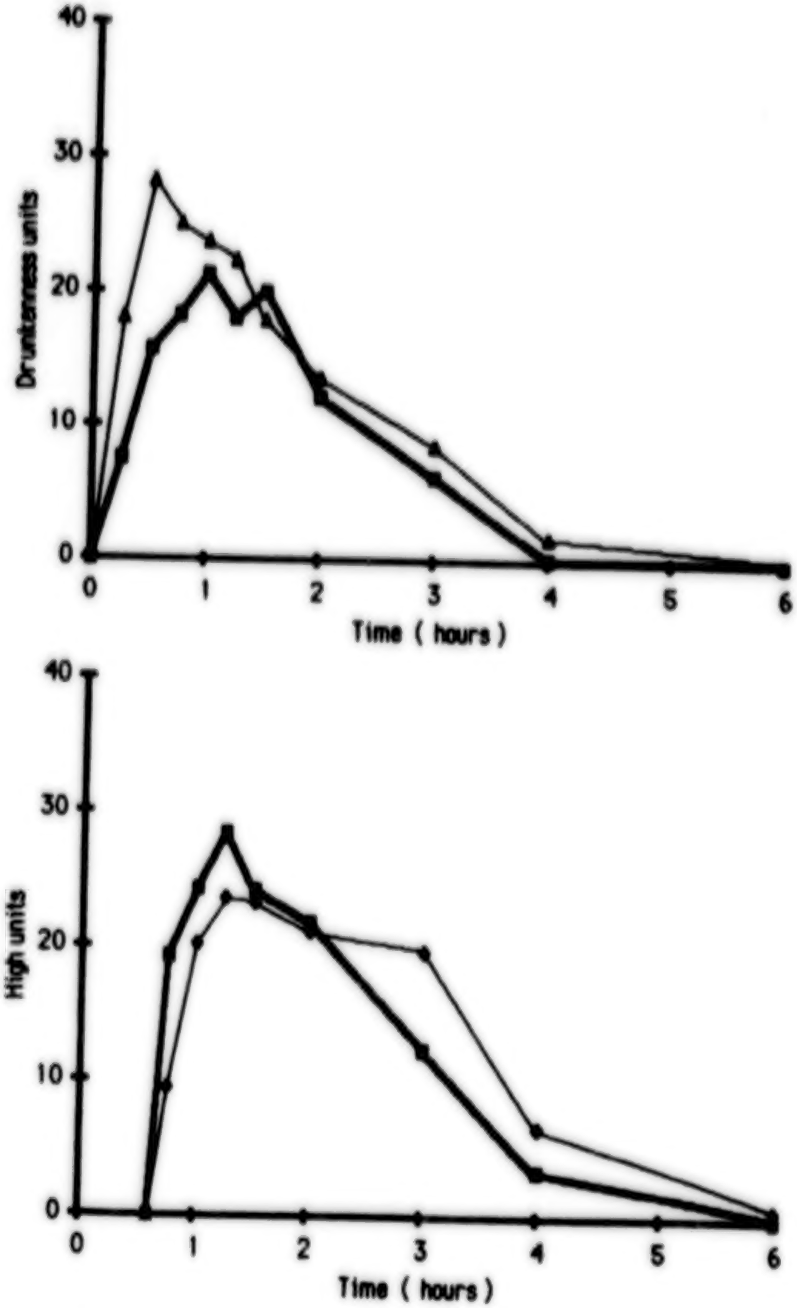
of the subjective effects of alcohol were simultaneously although separately studied from those of hashish. Figure 4 shows the self-evaluation report of the group of subjects who previously were aware of what they would later consume. The drunkenness estimation reported following intake of 0.5 g/kg of alcohol alone or together with hashish-tobacco cigarettes with an overall THC content of 2% is shown in the upper part of Figure 4. The self-evaluation report of effects of hashish in the group of subjects who consumed this substance alone or in combination with alcohol is shown at the bottom. The results of deceived subjects stand out (Figure 5). In these circumstances the changes reported were similar to the real situation of drug consumption.

In our case, expectancy may act as a good transducer of the subject's cultural conditioning factors. Before the experiments, the 96 selected subjects were asked to fill out a checklist designed to assess their individual experiences in the consumption of drugs and their perceptions of things and situations while under the effects of these substances. Although only subjects with a monthly pure alcohol consumption between 700 and 4000 ml were selected, those with the highest rates within this range anticipated fewer difficulties and a better performance of psychometric tests than the less experienced volunteers, who anticipated a greater dullness and deteriorated performance under similar circumstances.

Financial reward is the primary reason given by healthy volunteers who participate in pharmacological trials (Hasser *et al.*, 1977). It has been suggested that this subgroup of young people is characterized by a greater tendency to accept risks and to experience new perceptions. We do not know if this subpopulation reflects the subjective effects as do young people who consume drugs. We used the EPI questionnaire of Eysenck (Eysenck and Eysenck, 1975) to assess the personality characteristics of these participants (Camí *et al.*, unpublished data). Since 1981, 229 volunteers aged from 18 to 33 years (mean, 23 years) have been enrolled in different experiments with psychoactive drugs in our laboratory. Data were compared with a similar population of students from our university community and with reference values obtained by the author's questionnaire from a sample of the English population. The university student population was used to validate the questionnaire (R. Torrubia, personal communication). Our healthy volunteers reached higher scores in extravert and psychotic scales, suggesting that they are more open and social people who externalize their emotions more. Zuckerman (1983) reported that high scores in the extravert scale is a more common feature of impulsive subjects who like the experience of new feelings. Additionally, the lowest scores in the neurotic scale indicate that volunteers are emotionally more unstable people than the average and are more adaptable to certain risky and stressful situations, such as participation in clinical trials.

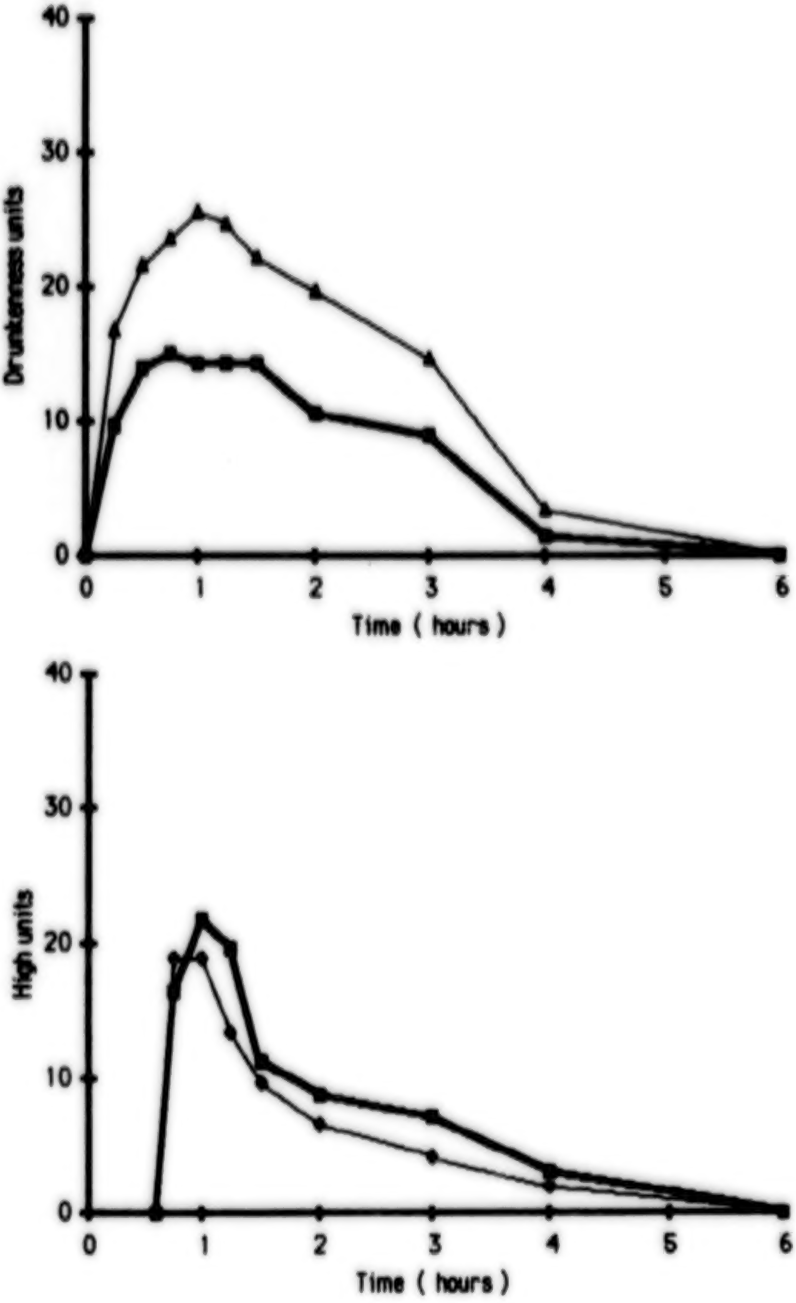
The observation of these nonpharmacological factors in studies performed in laboratories under very homogeneous methodological condi-

Figure 4



Time-course of drunkenness (upper) of hashish-high (bottom) following oral 0.5g/Kg of alcohol or 2% THC hashish-cigarette consumption (thin line) or both (thick line).

Figure 5



Time-course of drunkenness (upper) or hashish-high (bottom) following alcohol or hashish induced expectancy (thin line) or both (thick line).

tions, relates to a "second generation" of clinical pharmacology more closely oriented to the health care system as a natural laboratory (Editorial, 1986).

Pharmacokinetics as a Determinant of Drug Abuse

Recent studies have provided evidence of the important role played by pharmacokinetic factors in predicting drug abuse. Rapid delivery of drug to the central nervous system (CNS) should provide optimal pharmacokinetic conditions to encourage readministration. Certainly "crack" consumption through the respiratory route seems to be an example. The absorption rate and bioavailability are also pharmacokinetic determinants of drug abuse, and consequently conditioning factors for the preference of a particular substance over its analogues.

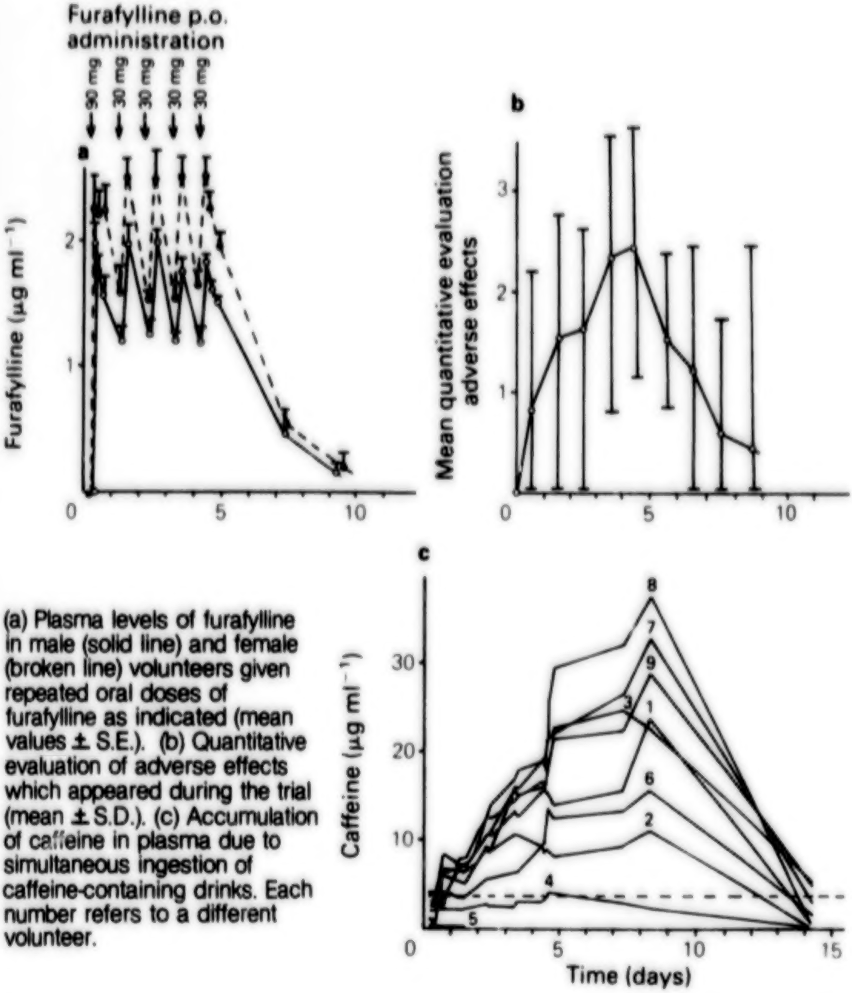
The pharmacokinetic properties that presumably contribute to persistent self-administration and abuse of drugs can be grouped into those that relate to acute "reinforcing" effects of a drug, to the development of physical dependence, and to the occurrence of withdrawal upon cessation of drug use (Busto and Sellers, 1986).

Our demonstration of unacceptable levels of adverse side effects resulting from a potent inhibiting effect of furafylline on caffeine metabolism in those volunteers drinking caffeine-containing beverages, has obvious implications in the field of development of new analogues (Tarrús *et al.*, 1987). When we were investigating the pharmacokinetics and tolerance of oral doses of furafylline, a "me-too" theophylline, despite constant plasma levels, the repeated administration of furafylline appeared to be associated with the onset of adverse xanthine-like side effects, a finding which was subsequently traced to the presence of, and possible synergism with, accumulated serum levels of caffeine (Figure 6). Another assay carried out in a volunteer receiving 100 mg of pure caffeine for seven days and one dose of furafylline on the fourth day (Figure 7) confirmed the presence of furafylline as the only factor needed for the accumulation to take place. Furafylline completely inhibits the microsomal hepatic metabolism of caffeine, the same phenomenon being general among 1,3,8-trisubstituted xanthines and not among 1,3-disubstituted xanthines, such as theophylline (Segura and Tarrús, 1984). This finding may have important implications in doping of sports, where the maximal accepted levels of caffeine consumption are controversial (World Symposium on Doping in Sport, 1987).

Conclusions

The parallel between designer drugs and "me-too" compounds led us to certain proposals. Regulatory agencies of all countries where commercialization of new psychoactive drugs is available, should require

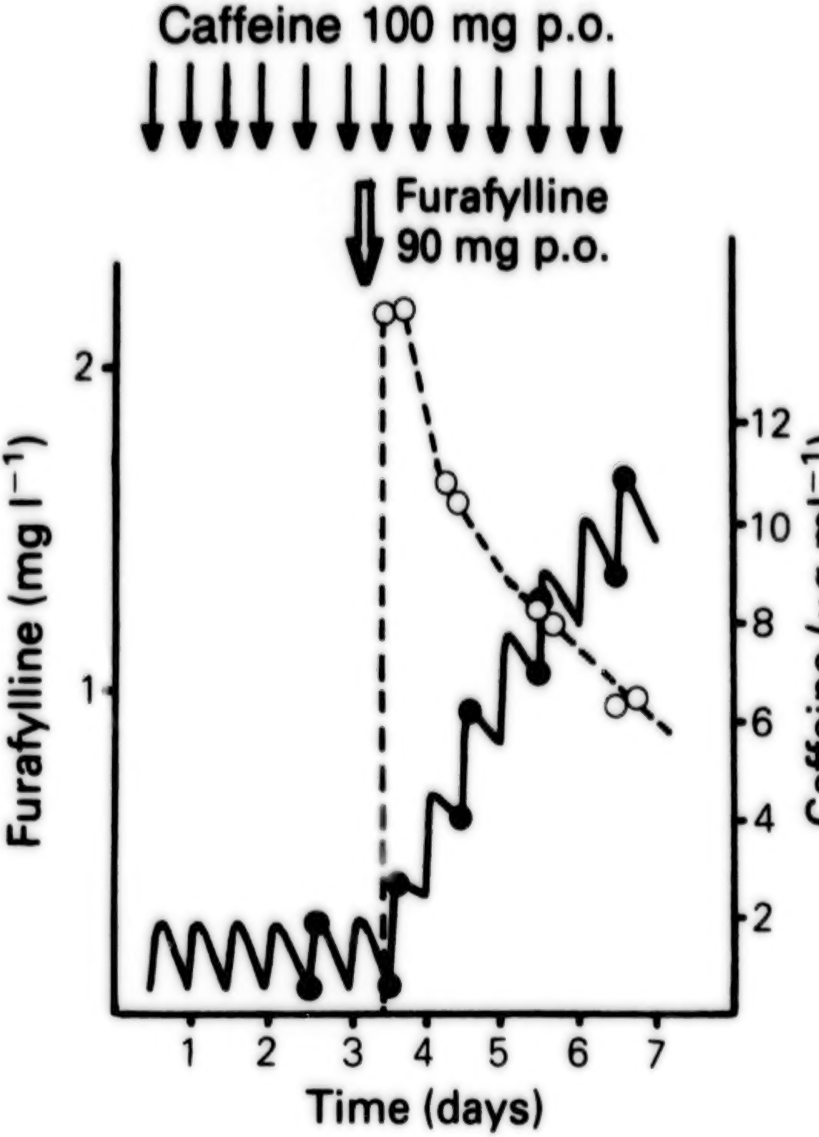
Figure 6



(a) Plasma levels of furafylline in male (solid line) and female (broken line) volunteers given repeated oral doses of furafylline as indicated (mean values ± S.E.). (b) Quantitative evaluation of adverse effects which appeared during the trial (mean ± S.D.). (c) Accumulation of caffeine in plasma due to simultaneous ingestion of caffeine-containing drinks. Each number refers to a different volunteer.

drug abuse liability testing. In this context, clinical pharmacology may play a substantial role in the extension of clinical dependence potential testing. In the future, an international consensus should establish the standardization of the procedures and the minimal requirements of preclinical and clinical drug abuse liability testing for regulatory and marketing purposes.

Figure 7



Plasma levels of furafylline (broken line) and caffeine (solid line) in one volunteer receiving repeated oral doses of caffeine and one single dose of furafylline as indicated.

References

Bovill, J.G., Which potent opioid? Important criteria for selection. *Drugs* 33: 520–530, 1987.

Busto U., Sellers E.M., Pharmacokinetic determinants of drug abuse and dependence. A conceptual perspective. *Clin. Pharmacokinetics* 11: 144–153, 1986.

Camí, J., Dependencia de benzodiacepinas. *Medicine (Barc)* 90: 501–506, 1987b.

Camí, J., Antó, J.M., Monteis, J., Alvarez-Lerma, F., Menoyo, E., Caus, F., and Farré, M., Monitoring cocaine epidemics in Barcelona. *Lancet* 2: 450–451.

Camí, J., Guerra, D., de la Torre, R., Ugena, B., Segura, J., Pérez-Reyes, M., Estudio psicofarmacológico de la interacción del hashish con el alcohol. Document presented to the U.S.-Spain Joint Commission for Scientific and Technical Cooperation, 3º año, 1987c.

Editorial. The natural laboratory. *Lancet* 2: 1019, 1986.

Eysenck, H.J., Eysenck, S.B.G., Manual of the Eysenck personality questionnaire. Hodder and Stougthton Educational, London, 1975.

Garattini, S., Tognoni, G. Notes on the future of clinical drug evaluation. In: J.L. Alloza (ed), Clinical and social pharmacology. Postmarketing period. Editio Cantor. Aulendorf, Federal Republic of Germany, 1985, pp 140–151

Guerra, D., Camí, J., de la Torre, R., Ugena, B., Segura, J., and Sanz, F., Pharmacological and subjective effects of alcohol intake. III World conference on Clinical Pharmacology and Therapeutics, Stockholm, July 27–August 1, 1986, abstract nº 1242.

Jasinski, D.R., Johnson, R.E., Henningfield, J.E., Abuse liability assessment in human subjects. *Trend Pharmacol. Sci.* May, 196–200, 1984.

Johanson, C.E., Woolverton, E.L., Schuster, C.R., Evaluating laboratory models of drug dependence. In: H.Y. Meltzer (ed.) Psychopharmacology: the third generation of progress. Raven Press, New York, 1987, pp 1617–1625.

Hassar, M., Pocelinko, R., Weintraub, M., Nelson, D., Thomas, G., Lasagna, L., Free living volunteer's motivations and attitudes toward pharmacologic studies in man. *Clin. Pharmacol. Ther.* 21: 515–519, 1977.

Henningfield, J.E., Lukas, S.E., Bigelow, G.E., Human studies of drugs as reinforcers. In: S.R. Goldbert and I.P. Stolerman, Behavioral analysis of drug dependence. Academic Press, Inc., Orlando, Florida, 1986, pp 69–122.

Marlatt, G.A., Rohsenow, D.J., Cognitive processes in alcohol use; expectancy and the balanced placebo design. In: N.K. Mello (ed.) Advances in substance Abuse: Behavioral and Biological Research, 1: 159–199, 1980.

Navarro, J., Lorente, S., Varo, J., Roig, M., El consumo de drogas en España. Cuadernos técnicos de toxicomanías nº 4, promovidos por la

Dirección General de Acción Social del Ministerio de Trabajo y Seguridad Social. Cruz Roja Española, Madrid, CIRSA, 1985.

Parlement Européen. The policies of the member states towards combating the drugs problem within the community. Série environnement, santé pubique et protection des consommateurs nº 9, 1986, p 51.

Segura, J., Tarrús, E. Severe inhibition of caffeine metabolism by xanthine derivatives. Proceedings of the Second European Congress of Biopharmaceutics and Pharmacokinetics 2: 520–528, 1984.

Tarrús, E., Camí, J., Roberts, D.J., Spickett, R.G.W., Celdrán, E., Segura, J., Accumulation of caffeine in healthy volunteers treated with furafylline. *Br. J. Clin. Pharmacol.* 23: 9–18, 1987.

World Pharmaceutical News. Review: 47 new chemical entities in 1986. Scrip, nº 1166/7, p 8, Dec. 25, 1986/Jan. 1, 1987.

World Symposium on Doping in Sport. International Amateur Athletic Federation and International Athletic Foundation, Florence, Italy, May 10–12, 1987.

Zuckerman, M., Sensation-seeking and sports. Personality and Individual Differences, 4: 285–293, 1983.

Assessment of Abuse Liability and Harm Liability of Drugs of Abuse

Tomoji Yanagita, M.D., Ph.D.

Introduction

The dependence potential and abuse liability of a drug including the ill effects due to its abuse form an important scientific basis for scheduling of drugs under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

For example, the former convention states that if a substance is liable to similar abuse and productive of similar ill effects as a drug in Schedule I or Schedule II, or is convertible into a drug in Schedule I or II, the World Health Organization (WHO) shall communicate that finding to the Commission on Narcotic Drugs (CND) of the Economic and Social Council of the United Nations. Under this convention heroin, morphine, cocaine, and cannabis can be regarded as the prototypic drugs in Schedule I, codeine as that of Schedule II, exemptable preparations are included under Schedule III, and heroin and cannabis are listed as well under Schedule IV.

Similarly, the latter convention says that if a substance has the capacity to produce similar abuse and similar ill effects as a substance in Schedule I, II, III, or IV, or has the capacity to produce a state of dependence and central nervous system stimulation or depression resulting in hallucinations or disturbances in motor functions or thinking or behavior or perception or mood, and is being or is likely to be abused so as to constitute a public health and social problem warranting international control, WHO shall communicate to the CND an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy. The major drugs presently scheduled under this convention are hallucinogens and tetrahydrocannabinols for Schedule I, amphetamines, some anorexiants, and methaqualone for Schedule II, short-acting barbiturates, glutethimide, and pentazocine for Schedule III, and long-acting barbiturates, meprobamate, some other anorexiants, and benzodiazepines for Schedule IV.

In view of the above scheduling criteria, data on dependence potential and the other pharmacological properties of a drug must be obtained for assessment of the likelihood of abuse of the drug (abuse liability) and the possible ill effects when abused (harm liability).

I. Assessment of Abuse Liability

The most important drug property relevant to the likelihood of abuse is the dependence potential of a drug. The dependence potential is also important to assess the harm liability of a drug. The dependence potential of a drug is predictable to some extent from its pharmacological similarity to those of prototypic drugs of abuse. Pharmacological profiles of several prototypic drugs of abuse are shown in Table 1. Generally speaking, the drugs that produce central nervous system stimulation or depression, and/or strong analgesia accompanied by potent behavioral effects are likely to produce dependence, and further study as described below may be needed.

A. Assessment of Dependence Potential

The WHO defines "drug dependence" in its technical report (WHO, 1969) as a state, psychic and sometimes also physical, resulting from taking a drug, characterized by behavioral and other responses that always include a compulsion to take a drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence.

As stated here, the essential state of dependence is the psychic dependence. It is well known, however, that in the case of such drugs as opiates, the development of physical dependence on these drugs may markedly enhance the drug-seeking and drug-taking behaviors. Therefore, when such enhancement is observable, the physical dependence can be said to influence the likelihood of abuse through enhancement of the psychic dependence. Thus, assessment of the physical dependence potential in this regard also becomes very important.

1. Psychic Dependence Studies in Animals

The most important effect of a drug relevant to its psychic dependence potential is the reinforcing effect on drug-seeking and drug-taking behavior. The ability of a drug to produce central nervous system stimulation or depression at self-administered dose levels is also important. These effects can be observed by self-administered experiments on drugs in animals. In addition, recent developments have made it possible to observe the subjective effects of a drug in comparison with those of the prototypic drugs in animals by drug discrimination experiments.

a. Self-administration Experiments

While various types of experimental methods for self-administration of drugs in animals are possible, the most widely used and basic method is that in which a fixed volume of drug preparation is automatically infused to an animal through an implanted catheter whenever the animal presses a lever available in its cage. Three standard procedures are usually used in the self-administration experiment: cross (or time-limited) self-

Table 1

Pharmacological Profile of Prototypic Drugs of Abuse

Drug	Gross behavior	Analgesic effect	Anticonvul. effect	Local anesthetic	Operant behavior effect
Morphine, Fentanyl	Sedation, Resp. Depress	Marked	None	Some	Suppress CAR[1]
Meperidine	Convulsion	Potent	None	Potent	Suppress CAR[1]
Pentazocine	Convulsion	Intermed.	None	None	RR[3] increase
Barbiturates, Methaqualone	Ataxia, Anesthesia	None	Potent	None	Prolong IRT[2]
Amphetamines	Hypermotility, Stereotypy	Intermed.	None	None	Shorten IRT[2]
Cocaine	Hypermotility, Convulsion	None	None	Marked	Shorten IRT[2]
LSD	Sedation, Hyperthermia	None	None	None	Premature R[4] Pause in FI
PCP	Stereotypy, Ataxia	Potent	None	None?	RR[3] increase

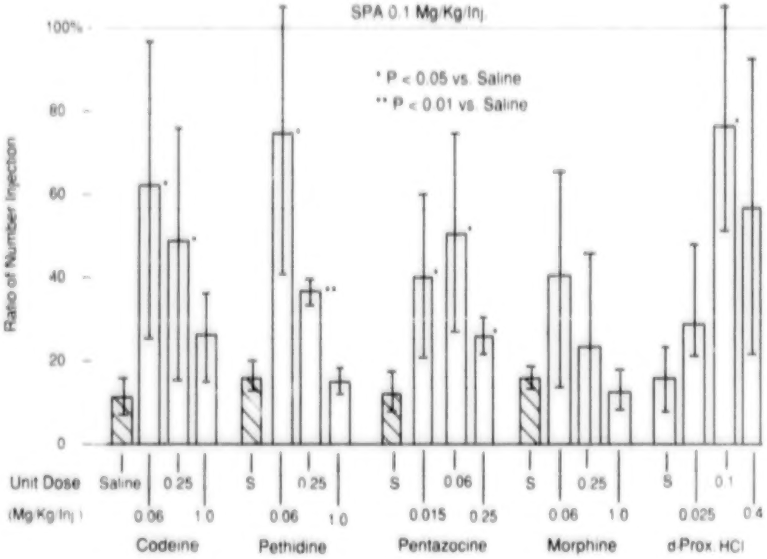
[1] Conditioned Avoidance Response.
[2] Inter-Response Time.
[3] Response Rate in FI schedule.
[4] Responses in Sidman avoidance.

administration, continuous self-administration, and progressive ratio experiments.

1) Cross Self-administration Experiments

In cross self-administration experiments, drug self-administration is available only for a limited period such as 15 minutes or four hours, during one or more sessions daily, and the intake rates are observed with a reference drug first, vehicle next, then a test drug at a certain unit dose, for two to four days each. This cycle is repeated for three to four unit doses. Various modifications of this procedure are possible, e.g. without the reference drug. This type of experiment has been conducted intensively by many investigators mostly in the rhesus monkey, and to a lesser extent in other species of animals such as the rat and dog. An example of the results obtained with several opioids and stimulants are shown in Figures 1 and 2 (Yanagita, 1977).

Figure 1



Results obtained in intravenous cross self-administration of several opioids with lefetamine (SPA) and saline in rhesus monkeys. The histograms represent the average self-administration ratio in 4-6 monkeys against lefetamine as 100%.

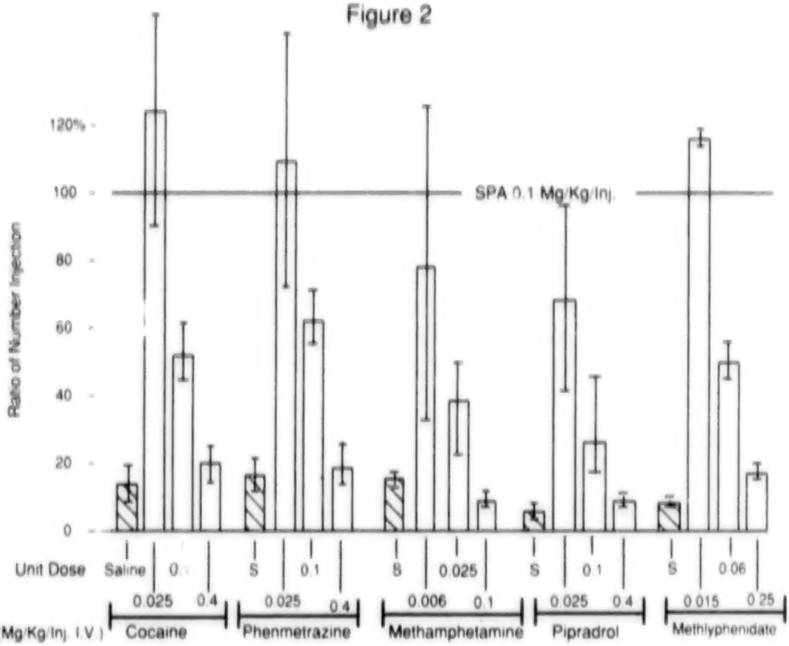
2) Continuous Self-administration Experiments

In continuous self-administration experiments, it is possible to observe not only the reinforcing effect but also

a) the property of a drug to produce overt signs of the effects at self-administered doses,

b) the average daily doses for a fixed period, and

Figure 2



Same as Figure 1 except the test drugs are stimulants here.

c) the trends of intake in the long term, i.e. whether increased, decreased, or unstable.

These findings will further serve for assessing tolerance and physical dependence potential as well as psychic dependence potential. The self-administration patterns observed in continuous experiments in rhesus monkeys on several prototypic drugs of abuse are shown in Table 2 (Yanagita, 1977).

Table 2

Continuous Self-Administration

Self-administration positive				**Negative**
Stable daily intake		**Erratic**		
Gradual Increase	**No increase**	**Frequent intake**	**Infrequent**	
Morphine Meperidine Codeine Pentazocine Pentobarbital [a] Alcohol [a]	Nicotine Diazepam Chlordiazepoxide [a]	Cocaine Amphetamines Volatile anesthetics [b]	Caffeine	LSD Mescaline STP (DOM) THC Nalorphine Saline

[a] Both intravenous and intragastric.
[b] Inhalation.

3) Progressive Ratio Experiments

Progressive ratio experiments are most relevant to an assessment of the psychic dependence potential of a drug, because reinforcing efficacy is assessed quantitatively. In the test, animals are obliged to press the lever an increasing number of times in order to receive each succeeding dose, and the lever-press ratio at the last obtained dose indicates the reinforcing efficacy (Yanagita, 1975; Brady *et al.*, 1977). Using this procedure the reinforcing efficacies of drugs can be determined and compared between classes of drugs. Comparison of efficacies under the physically dependent and non-dependent states should be made if a drug is found to produce physical dependence. An example of this obtained with morphine, cocaine and pentazocine in rhesus monkeys is shown in Table 3 (Yanagita, 1975).

Table 3

The Highest Lever Press Ratio for the Final Dose before Extinction

Drug (mg/kg/inj.)	Monkey	Dependent or Its Analogous State (A)	Control State (B)	A/B Ratio
Morphine 0.5[1]	#174[2]	1,600[3]	1,600	1
	#234	12,800	1,600[3]	8
	#248	12,800[3]	6,400	2
	#254	6,400	200[3]	32
Cocaine 0.11[1]	#281	800	1,600[3]	1/2
	#334	3,200[3]	6,400	1/2
Pentazocine 0.25[1]	#171	3,200	6,400[3]	1/2
	#364	3,200[3]	3,200	1
	#412	3,200	6,400[3]	1/2

[1] Unit-dose not adjusted each other.
[2] Self-maintained dose level of morphine was very low.
[3] Tested first.

b. Drug Discrimination Experiments

Drugs are usually abused because of their desirable subjective effects such as euphoria or feelings of elation, well-being, and contentment. It is thus important to observe such effects. In animals, however, observation of the subjective effects by verbal communication is impossible. Instead, experimental methods to assess the discriminative stimulus properties of drugs have been developed employing operant behavioral techniques. In such experiments, animals are trained to respond to the subjective effects of a training drug in a fixed manner, after which a test drug is administered and the animals' responses are observed. If the animals respond in the same manner as for the training drug (generalization), the subjective effects of the test drug are assumed to be similar, at least in part, to those of the training drug. Using such methods, intensive studies have been conducted on various psychotropic substances, mainly in the rat but also in the monkey. As for the results, animals were found to have similar discriminating capability to that of humans. In animals, this test has particular importance in assessing psychic dependence potential of some psychotropic substances which do not show any reinforcing effect in animal experiments. An example of the results obtained with several drugs in cocaine-trained rhesus monkeys is shown in Table 4 (Ando *et al.*, 1978).

Table 4

Generalization Test in Rhesus Monkeys Discriminating Cocaine

(0.1 mg/kg, i.v.) from Saline

Drug	Tested doses (mg/kg, i.v.)	Cocaine-like response (+: >60%)	
		No. 726	No. 742
Saline	0.2ml/kg	–	–
Morphine	0.05 - 0.4	+	+
d-Amphetamine	0.025- 0.4	+	+
Imipramine	0.05 - 3.2	+	–
Nicotine	0.05 - 1.6	+	–
Chlorpromazine	0.05 - 0.4	–	–
Pentobarbital-Na	4 - 16	–	–
Ethanol	100 - 400	–	–

2. Psychic Dependence Studies in Humans

a. Subjective Effects

The most widely used methods for this purpose are observation of some characteristic pharmacological effects and assessment of the subjective effects of a drug including liking of the drug. As subjects, persons experienced with drug abuse are desirable; however, naive subjects can also be used within limits. Several questionnaires such as the MBG/PCAG/LSD scales (morphine-benzedrine group/pentobarbital, chlorpromazine, alcohol group/LSD) of the Addiction Research Center Inventory (Haertzen, 1966) and POMS (profile of mood state; Johanson *et al.*, 1980a) are frequently used.

b. Reinforcing Effects

Several investigators have attempted to assess the reinforcing effects of opiates, sedative-hypnotics, and stimulants in humans by using various testing methods. For example, Griffiths *et al.* (1979) used former sedative abusers as subjects and tested choice preference among two dose sizes of pentobarbital, diazepam, or chlorpromazine, and placebo. The subjects were allowed to choose the drugs whenever they exercised with a stationary exercise bicycle for a 15-minute period. In the results, both pentobarbital and diazepam maintained self-administration, but not chlorpromazine or placebo. Studies similar to this were conducted on heroin (Mello, 1981), d-amphetamine, and diazepam (Johanson *et al.*, 1980a and 1980b).

B. Assessment of Physical Dependence Potential

The methods to assess the physical dependence potential of a drug are divided into two types of experiments. One is a cross dependence experiment in the subjects which are physically dependent on one of the prototypic drugs such as morphine or barbiturates, and the other is a physical dependence-producing experiment by repeated administration of a test drug to normal subjects.

1. Physical Dependence Studies in Animals

a. Cross Physical Dependence Experiments

The method to assess the cross-physical dependence potential of a drug in laboratory animals is well developed. The standard procedure is to make animals physically dependent on morphine, barbital, or some other drug, then withdraw the drug for a time, and administer a single dose of a test drug. If the test drug suppresses the withdrawal signs the drug is regarded to have that type of physical dependence potential. Such opioids as heroin, pethidine, methadone, and codeine will suppress morphine withdrawal signs, and many sedative-hypnotics including ben-

Table 5

Physical Dependence Potential of Several Potent Analgesics and Related Drugs Tested in Rhesus Monkeys

	Cross physical dependence			
	Suppression of morphine withd.*	Precipitation of morphine withd.	Complete suppression (mg/kg)	Physical dependence-producing property
Morphine	+	−	3.0 sc	+ + +
Methadone	+	−	3.0 sc	Untested
Oxymethebanol	+	−	3.0 sc	+ + +
Meperidine	+	−	10.0 sc	+ + +
Codeine	+	−	16.0 sc	+ + +
d-Propoxyphene	+	−	16.0 sc	+ +
Thebaine	−	+		+ +
Azabicyclane	−(+)**	+		+ + +
Propiram	−(+)	+		+ +
Pentazocine	−(+)	+		+
Naloxone	−(−)	+		−

* Dependent on morphine—3 mg/kg x 4/day. ** Dependent on morphine—0.3 mg/kg x 4/day.

Table 6

Physical Dependence Potential of Several Sedative-Hypnotics Tested in Rhesus Monkeys

Drugs	Cross physical dependence* Suppression of barbital withdrawal	Cross physical dependence* Complete suppression (mg/kg)	Physical dependence producing property
Barbital	+	75 po	+ +
Pentobarbital	+	>25 iv	+ +
Alcohol	+	4,000 po	+ +
Chloroform	+		Untested
Meprobamate	+	>200 po	+ +
Diazepam	+	5 po	+ +
Chlordiazepoxide	+	20 po	+ +
Oxazolam	+	20 po	—
Chlorpromazine	—	—	—
Perlapine	—	—	—

*Dependent on barbital and withdrawn (75 mg/kg x 2 per day po).

zodiazepines will suppress barbital withdrawal signs (Tables 5, 6; Yanagita, 1973).

b. Physical Dependence-Producing Experiments

Physical dependence on a drug can be experimentally developed by repeated administration of a test drug to normal animals. The necessary administration period ranges from three days to several weeks depending on the type of drug, dose size, dose interval, administration route, and animal species. Development of physical dependence on a test drug is observed through manifestation of withdrawal signs by either terminating the drug administration or administering an antagonist to the animals if it is available. The major withdrawal signs observable with opioids are body weight loss, diarrhea, anorexia, vomiting (except in the rat), hyperirritability, tremor, and muscle rigidity. Death due to dehydration can be seen occasionally. The withdrawal signs with sedative-hypnotics are characterized by hyperirritability, tremor, body weight loss, anorexia, muscle rigidity, convulsions, and a delirium-like state. The degree of physical dependence potential is evaluated from the severity of the withdrawal signs (Yanagita, 1973).

2. Physical Dependence Studies in Humans

In the past, test methods on opioids similar to both the cross physical dependence and physical dependence-producing experiments in animals were applied to former opiate dependent subjects, with lower doses and shorter administration periods in humans (Fraser *et al.*, 1961). As a recent trend, however, these tests are rarely conducted unless the physical dependence potential of a drug is predicted to be practically nil or very low from animal experiments and confirmation of the animal findings in humans is necessitated.

Useful information on the physical dependence potential of therapeutics can be obtained in clinical trials on the drug such as those of phase 3 (multiple clinical trials) or in a practical use as in phase 4 studies (post-market surveillance). In the case of opioids, withdrawal signs such as yawning, lacrimation, rhinorrhea, perspiration, muscle tremors, pupil dilatation, goose flesh, anorexia, hyperpnea, restlessness, insomnia, elevation of blood pressure, emesis, diarrhea, and weight loss, and in the case of sedative-hypnotics such withdrawal signs as depression, aggravation of psychosis, agitation, insomnia, anorexia, nausea, tremor, grand mal seizures, and delirium are known to be manifested in those who abused heroin, morphine, barbiturates, or alcohol.

3. Prediction of Abuse Liability

If a drug fulfills the following criteria its likelihood of abuse may be high:

1) Its pharmacodynamic profile and subjective effects (or discriminative stimulus properties) in animals or humans are similar to those of any prototypic drug of abuse, or

2) it is self-administered by animals under either the physically dependent or non-dependent state or is liked by human subjects, to the extent that in reinforcing efficacy it is comparable to the prototypic drugs, and

3) overt signs of the drug effects are observable in the self-administering subjects when the drug is made freely available, and

4) its properties such as dosage form, stability, solubility, odor, and taste as well as its availability are within a range allowing the drug to be practically abused.

It should be noted, however, that a drug that fulfills the above criteria may not necessarily actually be abused. Interest in the drug and knowledge of its effects are also prerequisite. Good examples can be seen in the cases of marihuana and organic solvents where, in spite of their historic availability, widespread abuse of these substances was scarcely known of in developed countries until the 1950's.

II. Assessment of Ill Effects

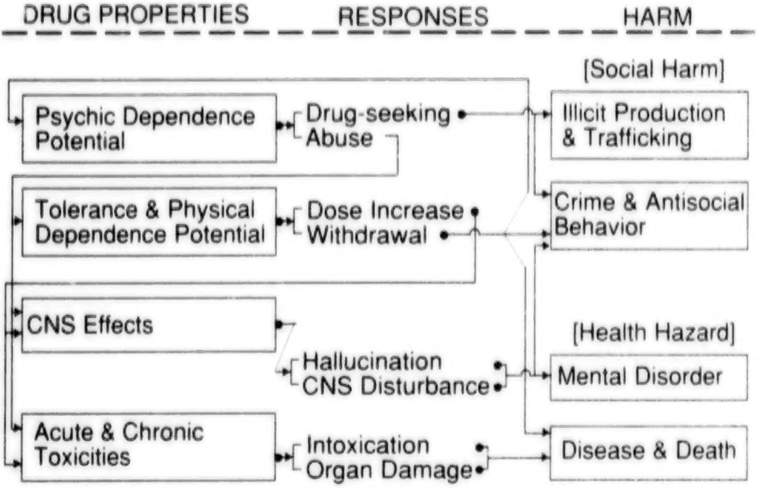
If a drug has a high abuse liability, the drug is likely to be abused, and once abused the harm due to abuse may be developed. The ill effects due to abuse of a drug can be predicted to some extent by comparing the dependence potential and pharmacological and toxicological properties of the drug in question with those of the prototypic drugs of abuse.

A. Relationship between Drug Properties and Ill Effects

The harm that is developed as a consequence of abuse is primarily attributable to the pharmacological, toxicological, and dependence-producing properties of a drug including its impurities. Therefore, an analytical observation of the relationship between the types of drug properties and ill effects will be considered in this section (Figure 3; Yanagita, 1986).

Figure 3

Drug Properties and Harm Due to Abuse



Relationship between the drug properties of dependence-producing drugs and the ill effects due to their abuse. The dependence characteristics and ill effects are somewhat specific to each class of drugs, such as opiates, sedative-hypnotics, stimulants, and hallucinogens, and also to each drug within the class.

1. Psychic Dependence Potential

Psychic dependence potential is the capacity of a drug to produce a state of psychic dependence which is characterized by both compulsive drug-seeking and drug-taking behavior in the subject who has experienced the pharmacological effects of the drug, and/or by the state of experiencing the effects of the drug. The major pharmacological determinants of psychic dependence potential are the efficacy of a drug to reinforce the drug-seeking and drug-taking behaviors, and the subjective effects of the drug which are the target of its abuse. The psychic dependence potential is an essential pharmacological property of a drug constituting its abuse liability and resulting in compulsive drug-seeking and repeated or spree use of drugs. The compulsive drug-seeking leads to antisocial behavior including crime involved in obtaining the drug, and demand for a drug results in development of illicit production and trafficking. Once a drug is abused many other pharmacological and toxicological properties as listed below become relevant to various kinds of ill effects.

2. Central Nervous System Effects

The pharmacological effects of drugs, particularly the central nervous system effects including psychotoxic effects, are closely related to the ill effects of abuse because unusual mental states and antisocial behavior including tendencies to criminal and dangerous behavior may be developed due to the pharmacological effects of drugs.

3. Tolerance and Physical Dependence Potential

The repeated use of a certain class of drugs such as opiates or barbiturates results in development of tolerance and physical dependence. The development of tolerance may lead to an increase in the abused dose which may result in exaggeration of toxic responses to the drug. When a drug has relatively potent acute lethal effects, and tolerance has been rapidly lost because of a short-term withdrawal, reuse at the previous dose frequently results in sudden death, which is one of the serious public health problems in the abuse of the opiates and some other drugs.

Physical dependence is also relevant to the ill effects if the withdrawal manifestation is physically or psychically hazardous. Sometimes the manifestation may be life-threatening due to such causes as homeostatic failure and/or convulsions. These ill effects are primarily part of the health problem, but psychotic withdrawal manifestation may also relate to social problems because of development of antisocial or dangerous behavior.

4. Acute Toxicity and Organ Toxicity

Acute toxicity and organ toxicity of drugs often become the cause of death and/or health injury. For example, respiratory or cardiac failure or convulsions may occur due to the acute toxic effects of opiates, barbiturates, stimulants, or some hallucinogens, and frequently these become the cause of sudden death. Some drugs such as barbiturates and alcohol are known to produce hepatic damage due to their chronic toxicities. Thus, abuse of these drugs produces serious public health problems.

B. Prediction of Ill Effects

The ill effects that are likely to be developed as a consequence of abuse can be categorized as public health problems and social problems. As public health problems, such medical problems as injury and death due to intoxication, mental disorders, and/or organ damage occur. Antisocial behavior including crime due to the drug-seeking behavior and pharmacological effects of drugs is the primary social problem which induces other social problems such as illicit production and illicit trafficking of drugs. The public health problems are primarily attributable to individual ill effects of a drug, and the social problems are attributable to social ill effects.

1. Individual Ill Effects

The most important determinant for the ill effects includes the route of administration and dose involved in abuse. These can be roughly predicted from the self-administration data mostly available in animals and to some extent in humans. Once these factors are estimated, it is not so difficult to predict the possible individual ill effects, physical, psychic, and behavorial, from pharmacological, psychopharmacological, and toxicological data. If a drug is known to produce opiate or barbiturate-like severe withdrawal signs, serious physical or psychic ill states may be developed during the withdrawal following heavy use of the drug. Sudden death attributable to the acute toxicity of a drug is likely to occur in its abuse if the drug has high potentials in tolerance development and lethal effects.

2. Social Ill Effects

As in the case of individual ill effects, the route of administration and dose are essential determinants for prediction of social ill effects. In addition to possible development of antisocial behavior due to the direct drug effects and also to the psychotoxic manifestation during withdrawal, persistent drug-seeking behavior due to strong psychic dependence on the drug may also result in certain types of antisocial behavior subsequently leading to illicit production and/or trafficking of the drug. In this sense assessment of the psychic dependence potential of a drug is extremely important, as is the psychotoxicity of the drug at self-administered dose regimens.

Bibliography

Ando, K. and Yanagita, T. The discriminative stimulus properties of intravenously administered cocaine in rhesus monkeys. In: Colpaert, F.C. and Rosecrans, J.A., eds. Stimulus properties of drugs: ten years of progress. Amsterdam: Elsevier/North-Holland Biomedical Press, 1978.

Brady, J.V. and Griffiths, R.R. Drug-maintained performance procedures and the assessment of drug-abuse liability. In: Thompson, T. and Unna, K.R., eds. Predicting dependence liability of stimulant and depressant drugs. Baltimore: University Park Press, 1977.

Fraser, H.F., Van Horn, G.D., Martin, W.R., Wolbach, A.B., and Isbell, H. Methods for evaluating addiction liability, *J. Pharmacol. Exp. ther.*, 133; 371–387, 1961.

Griffiths, R.R., Bigelow, G., and Liebson, I. Human drug self-administration: double-blind comparison of pentobarbital, diazepam, chlorpromazine and placebo, *J. Pharmacol. Exp. ther.*, 210: 301–310, 1979.

Haertzen, C.A. Development of scales based on patterns of drug effects, using the Addiction Research Center Inventory (ARCI). *Psychol. Rep.*, 18: 163-194, 1966.

Johanson, C.C. and Uhlehugh, E.H. Drug preference and mood in Humans: Diazepam. *Psychopharmacol.*, 71:269-273, 1980a.

Johanson, C.E. and Uhlehugh, E.H. Drug preference and mood in humans: d-amphetamine. *Psychopharmacol.*, 71:275-279, 1980b.

Mello, N. 1981 (personal communication).

Yanagita, T. An experimental framework for evaluation of dependence liability of various types of drugs in monkeys, *Bull. Narcotics.* XXV: 57-64, 1973.

Yanagita, T. Some methodological problems in assessing dependence-producing properties of drugs in animals. *Pharmacol. Review,* 27: 503-509, 1975.

Yanagita, T. Brief review on the use of self-administration techniques for predicting drug dependence potential. In: Thompson, T. and Unna, K.R., eds. Predicting dependence liability of stimulant and depressant drugs. Baltimore, University Park Press, 1977.

Yanagita, T. Dependence characteristics and risk assessment of agonist-antagonist analgesics. WHO Symposium on Drug Dependence: Benefit-Risk Ratio Assessment of Agonist-Antagonist Analgesics, Stockholm, Aug. 2, 1986. In: Johanson, C.C. and Yanagita, T., eds. *Drug and Alcohol Dependence,* in New York, Elsevier Science Publisher.

WHO expert committee on drug dependence: 16th report. Wld Hlth Org. techn. Rep. Ser., No. 407, 1969.

Public Health Risks Resulting from Processing Impurities in Clandestine Drugs

Michael Klein, Ph.D.

Introduction

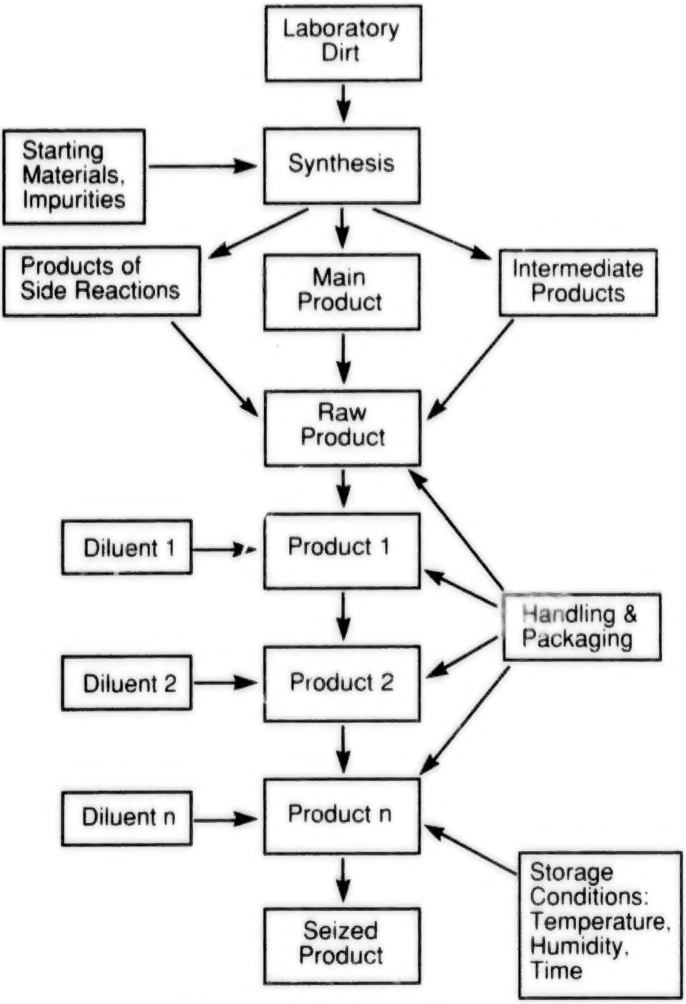
Pharmacological and toxicological data on many of the impurities in illicit clandestinely manufactured drugs is limited or nonexistent. Much of the toxicological data that is currently available in the literature relates to prototypes of the chemical class and not to the individual chemical entity which has been found in the illicit drug sample. Therefore, only likely effects of the impurities are known and these are only projections owing to similarities in their chemical structures to those of related standard compounds. Additionally, only a few laboratories around the world are actively engaged in elucidating the molecular structures of these impurities in illicit drugs—and perhaps even fewer that are studying the adverse effects that they may cause. Therefore, the term, "public health risk potential", is probably more appropriate when applied to these substances than "public health risk." The following represents an overview highlighting some of the current literature in this area.

Characteristics of Impurities

As a chemical reaction proceeds, various impurities are formed which accumulate because of the lack of quality control in illicit manufacture and are present in the finished drug product. These include reactants, by-products, intermediates and contaminants within reagents. The impurities may provide significant clues towards the characterization of a manufacturing process. Research on the identification of low level impurities in illicit drugs, often performed by forensic laboratories, has been used to develop "chemical signatures" for illicit drugs (Lambrechts, *et al.,* 1984, 1986; Strömberg, *et al.,* 1975; 1983). The purpose of signatures is to provide useful intelligence data related to the clandestinely produced drug. The chemical signature provided by these impurities may be used for direct comparison of illicit drug samples, i.e., to try to link different samples to a common origin. Additionally, the chemical signature (or the impurities present) is sometimes useful in determining the method of synthesis of the clandestine drug or for comparing samples of drugs seized from different locations.

Figure 1

Origin of Impurities in Illicit Drugs (Strömberg and Maehly, 1979).



The simplified schematic in Figure 1 (Strömberg and Maehley, 1979) shows the origins of potential impurities in illicit drugs. Impurities are shown arising from laboratory equipment; there are contributions from the starting materials and impurities in the precursors and essential chemicals; there are contributions from side reactions, as well as from intermediate products in multi-step reaction schemes. The impurities formed in side reactions are the ones which can be useful in determining the method(s) of synthesis. Impurities resulting from handling and packaging procedures and the addition of diluents, on the other hand, are derived from subsequent treatments of the raw product in the clandestine laboratory. Other factors which can produce impurities in the drug are related to the conditions under which the illicit drug may be stored. Conditions such as temperature, humidity, and time may effect the nature of the impurities present in the drug product. Table 1 lists impurities found in illicit heroin samples that result from the reaction of acetic anhydride with morphine which contains impurities many of which are naturally-occurring in opium as well as those which may result from oxidation of morphine, that is, morphine N-oxide (Klein, 1977).

The diluents and adulterants used in illicit drug preparations represent a variety of chemical and pharmacological classes (Nair *et al.*, 1986). These include central nervous system stimulants as well as depressants. Some diluents and adulterants which have been used with illicit drugs are sugars, caffeine, antipyrine (phenazone), ascorbic acid, ephed-

Table 1

Some heroin manufacturing impurities

(Moore *et al*, 1986; Allen *et al* 1984; Klein, 1977)

1. Meconin
2. Hydrocotarnine
3. 3,6-dimethoxy-4,5-epoxyphenanthrene
4. Thebaol
5. O^4-acetylthebaol
6. 4,6-diacetoxy-3-methoxyphenanthrene
7. (E)-3-[2-(2-N-methylacetamido)ethyl)-4,5-methylenedioxy-6-methoxyphenyl] acrylic acid
8. Papaverine
9. O^6,N-diacetyl-α-norcodimethine
10. O^6,N-diacetyl-α-normorphimethine
11. O^6,N-diacetylnorcodeine
12. N-acetylnormorphine
13. O^3,O^6,N-triacetyl-α-normorphimethine
14. O^6,N-diacetylnormorphine
15. 4-acetoxy-3,6-dimethoxy-5-[2-(N-methylacetamido)]ethylphenanthrene
16. O^3,O^6-N-triacetylnormorphine
17. 4,6-diacetoxy-3-methoxy-5-[2-(N-methylacetamido)]-ethylphenanthrene
18. N-acetylnorlaudanosine
19. Papaveraldine
20. Desthebaine
21. 4,8-diacetoxy-3-methoxy-8-[2-(N-methylacetamido)]-ethylphenanthrene
22. Narcotine
23. 4-acetoxy-3,6-dimethoxy-8-[2-(N-methylacetamido)]-ethylphenanthrene
24. N-acetylnornarcotine
25. 4,6-diacetoxy-3-methoxy-8-[2-(N-methylacetamido)]-ethylphenanthrene
26. (E)-N-acetylanhydronornarceine
27. (1R,9S)-1-acetoxy-N-acetyl-1,9-dihydroanhydronornarceine
28. (Z)-N-acetylanhydronornarceine
29. (1R,9R)-1-acetoxy-N-acetyl-1,9-dihydroanhydronornarceine
30. O^3-monoacetylmorphine
31. O^6-monoacetylmorphine
32. 4-acetoxy-3,6-dimethoxyphenanthrene
33. N,O^6diacetylnorcodeine

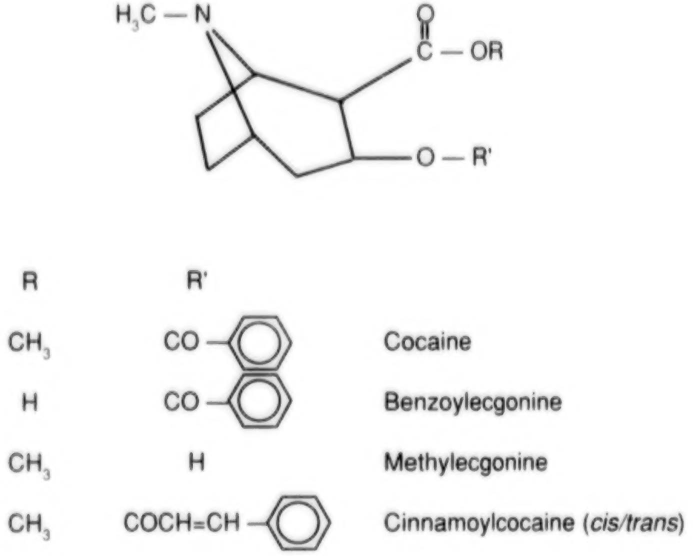
rine, barbituric acid derivatives, lidocaine, and procaine. Since these substances have extensively different pharmacologic activities, a review of their potential public health risks is outside the scope of this paper and is not included herein.

The present discussion focuses on those impurities in illicit drugs that are formed in the drug's manufacturing process and not those substances added to the drug product. These impurities attributed to the anticipated lack of quality control in the illicit laboratories are shown in Figure 1. An additional potential problem may result from the organic solvents used in processing illicit cocaine from the coca leaf (Boon, 1987). The solvents are used in extraction of cocaine from the leaf and in converting the base form to cocaine hydrochloride; they include toluene, acetone, ethyl ether and other organic chemicals. Trace amounts of these substances are trapped in the cocaine and are present along with other naturally-occurring alkaloids (Figure 2).

A considerable amount of the current concern about impurities in clandestinely produced drugs results from the notoriety gained by the impurity, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), formed in the synthesis of the reversed ester analogue of meperidine (pethidine)

Figure 2

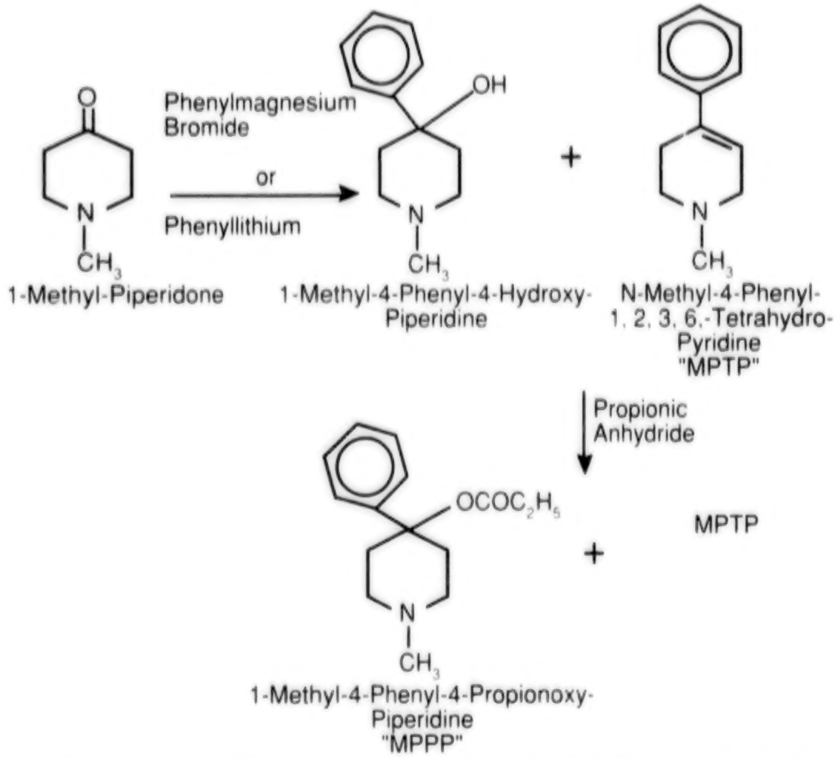
Some Naturally-Occurring Alkaloids in *Erythroxylon Coca*



—1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) (Figure 3). MPTP, a fairly simple molecule, has been found to be responsible for producing irreversible parkinsonism in those individuals who have taken MPTP-contaminated MPPP as a heroin substitute. Extensive and detailed descriptions of MPTP have been covered elsewhere by Dr. R. Stanley Burns (1987) and others. (Davis, *et al.*, 1979; Fellman and Nutt, 1985; Langston, *et al.* 1983 and 1984; Lieberman, 1987, Wright, et al, 1984; Shih and Markey, 1986; and Williams, 1984).

Figure 3

Synthesis of MPPP and MPTP


O
Phenylmagnesium Bromide
or
Phenyllithium
OH
+
N
CH3
1-Methyl-Piperidone
1-Methyl-4-Phenyl-4-Hydroxy-Piperidine
N-Methyl-4-Phenyl-1, 2, 3, 6,-Tetrahydro-Pyridine "MPTP"
Propionic Anhydride
OCOC2H5
MPTP
1-Methyl-4-Phenyl-4-Propionoxy-Piperidine "MPPP"

Methamphetamine and Amphetamine

A major focus of research on processing impurities of illicit drugs has been related to the development of chemical signatures (Strömberg, 1975, 1983). Many of the impurities in methamphetamine and amphetamine samples have been useful in determining methods of their syntheses (Van der Ark *et al.*, 1978; Sinnema and Verweij, 1981). Some of the impurities which have been isolated from illicit methamphetamine samples (that originate within the United States) contain the precursors methylamine, formic acid, N-methylformamide and phenylacetone (Lomonte *et al.*, 1976; Barron *et al.*, 1974; Kram and Kruegel, 1976; Kram, 1979). It is reasonable to expect that all precursors to some extent would be present in the illicit drug. On occasion, demand for precursors themselves are the products of clandestine manufacture. Therefore, the toxicity of precursors of precursor chemicals may be an important consideration. For example, the toxicity of benzyl chloride has been documented (Abdel-Rahman *et al.*, 1986) and benzyl chloride has been shown to be used as a precursor of benzyl cyanide which in turn is converted to phenylacetic acid which in turn is converted to phenylacetone to manufacture methamphetamine in clandestine laboratories (Unpublished data).

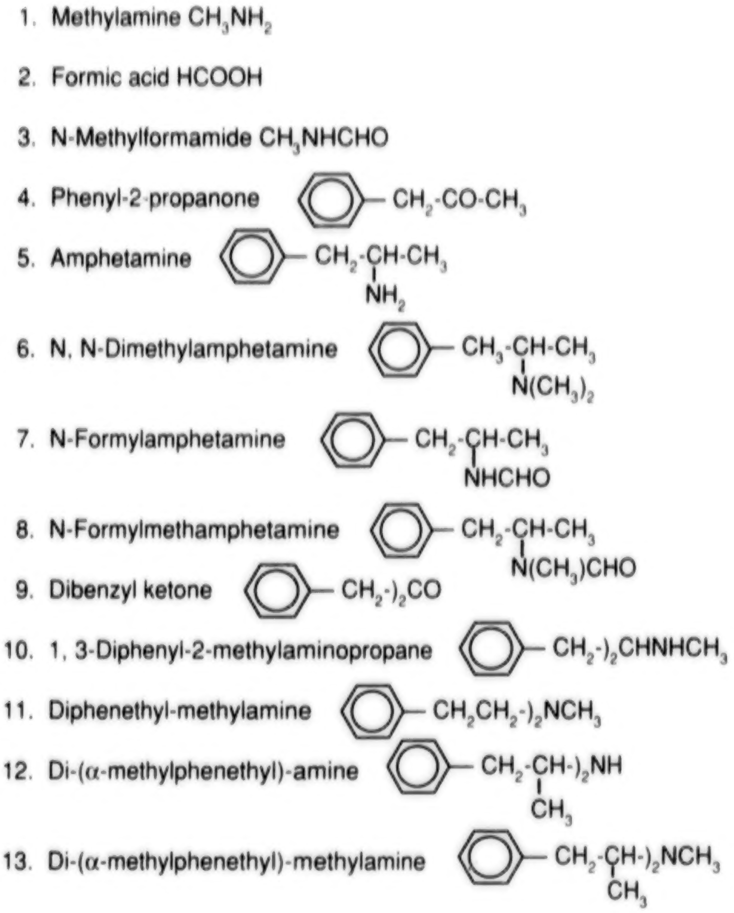
The presence of amphetamine and N,N-dimethylamphetamine in the methamphetamine sample stems from the presence of ammonia and dimethylamine, respectively, impurities in the precursor chemical, methylamine (Kram and Kruegel, 1976) (See Figure 4). N-Formylmethamphetamine is an intermediate in the synthesis which is specific to the Leuckart reaction. The presence of N-formylamphetamine results from the impurity of ammonia in methylamine, analogous to the formation of amphetamine. The remaining substances in Figure 4 result from further reaction of the intermediate product with additional phenylacetone. The basic Leuckart reaction, giving rise to these impurities and others, including alpha-benzylphenethylamine in amphetamine and alpha-benzyl-N-methylphenethylamine in methamphetamine, is shown in Figure 5. The reaction takes place in two steps: first reaction of phenylacetone with N-methyl formamide, or formic acid with methylamine, gives the intermediate, N-formylmethamphetamine. Secondly, N-formylmethamphetamine is reacted with acid to obtain methamphetamine. This reaction is nonstereospecific and a chiral center at the reactive carbon atom is introduced. Therefore, the racemate of dl- or RS-methamphetamine is formed. The origin of alpha-benzyl-N-methylphenethylamine in methamphetamine stems from the synthesis of phenylacetone from phenylacetic acid. Preparation of phenylacetone from phenylacetic acid gives dibenzyl ketone which if not removed (and often it is not), upon its reaction in the Leuckart process gives alpha-benzyl-N-methylphenethylamine. The analogous by-product, alpha-benzylphenethylamine, has also been found in illicit amphetamine which has been produced by the Leuckart method.

Relative toxicity of the amphetamines and corresponding alpha-benzylphenethylamines were compared by determining the LD-50's (Lethal Dose-50) and the CD-50's (Convulsive Dose-50) in mice for each of the four compounds (Noggle *et al.*, 1985). Mortality was determined after twenty-four hours for the LD-50 measurement and convulsions were defined as a mixture of tonic-clonic type seizures of at least three to five seconds in the CD-50 study. Data for amphetamine and methamphetamine were determined using enantiomeric pairs. Both alpha-benzyl compounds exhibited lower LD-50's than did dl-amphetamine. In these studies, it was noted that the animals treated with the alpha-benzyl com-

Figure 4

Some Methamphetamine Impurities

(Kruegel *et al.*, 1976)



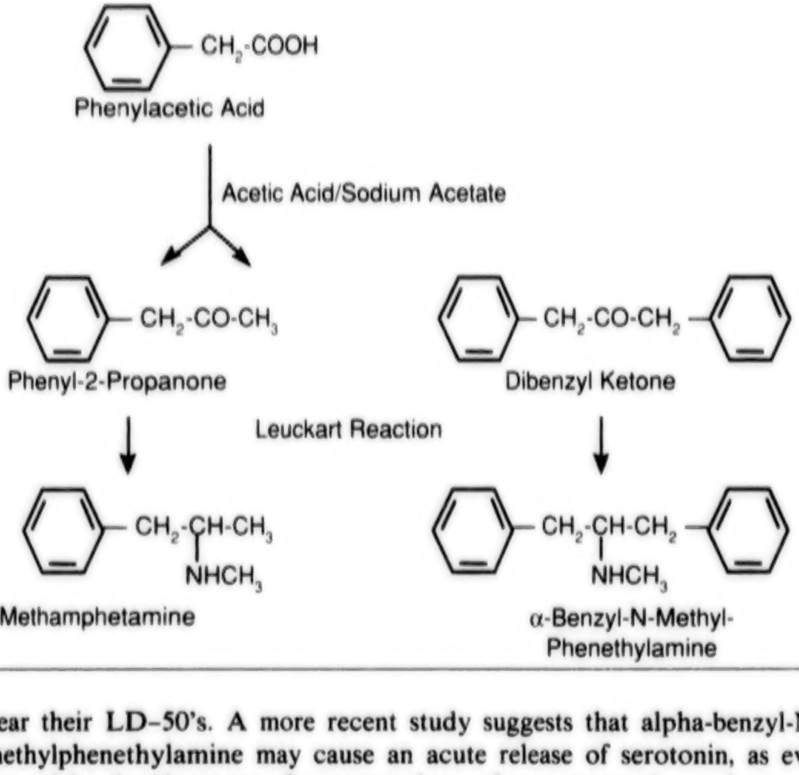
1. Methylamine CH_3NH_2
2. Formic acid HCOOH
3. N-Methylformamide CH_3NHCHO
4. Phenyl-2-propanone $CH_2\text{-}CO\text{-}CH_3$
5. Amphetamine $CH_2\text{-}\underset{NH_2}{CH}\text{-}CH_3$
6. N, N-Dimethylamphetamine $CH_3\text{-}\underset{N(CH_3)_2}{CH}\text{-}CH_3$
7. N-Formylamphetamine $CH_2\text{-}\underset{NHCHO}{CH}\text{-}CH_3$
8. N-Formylmethamphetamine $CH_2\text{-}\underset{N(CH_3)CHO}{CH}\text{-}CH_3$
9. Dibenzyl ketone $CH_2\text{-})_2CO$
10. 1, 3-Diphenyl-2-methylaminopropane $CH_2\text{-})_2CHNHCH_3$
11. Diphenethyl-methylamine $CH_2CH_2\text{-})_2NCH_3$
12. Di-(α-methylphenethyl)-amine $CH_2\text{-}\underset{CH_3}{CH}\text{-})_2NH$
13. Di-(α-methylphenethyl)-methylamine $CH_2\text{-}\underset{CH_3}{CH}\text{-})_2NCH_3$

pounds exhibited very different nonlethal symptoms compared with animals given the corresponding amphetamines. In doses well below the LD-50, animals treated with the alpha-benzyl compounds experienced convulsions characterized by clonic and tonic seizures.

The CD-50 for an alpha-benzylphenethylamine is significantly lower than its corresponding LD-50. In contrast, the CD-50 for amphetamine is essentially equivalent to its LD-50. This indicates that the alpha-benzyl compounds caused greater central nervous system stimulation at the brain stem and spinal cord, as noted by tonic and clonic seizures (Noggle *et al.*, 1985). The convulsions are seen with the primary cortical stimulants, amphetamine and methamphetamine, only at doses which are at or

Figure 5

Synthesis of Methamphetamine and α-Benzyl-N-Methylphenethylamine From Phenylacetic Acid



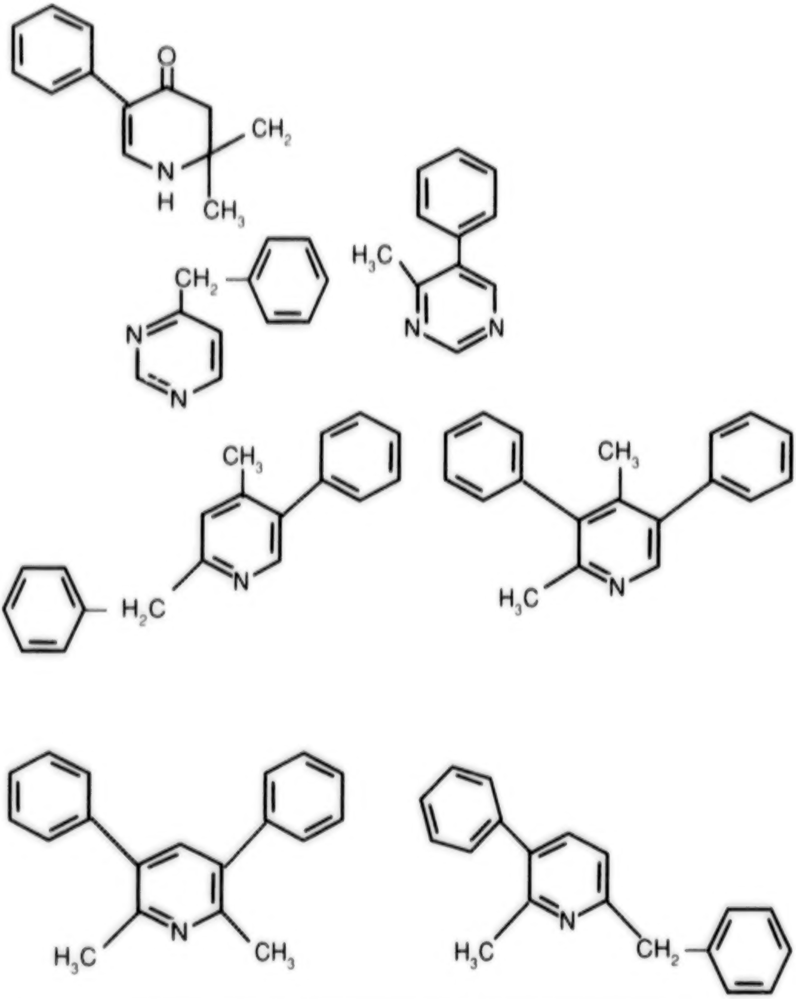
near their LD–50's. A more recent study suggests that alpha-benzyl-N-methylphenethylamine may cause an acute release of serotonin, as evidenced by development of symptomalogy of a serotonergic syndrome in rats (Cadet *et al.*, 1988). The authors propose further studies in order to determine whether there is any correlation between observed behaviors and biochemical changes in the brain.

Another group of impurities identified in illicit amphetamine samples are the pyrimidine and pyridine derivatives shown in Figure 6 (Van der Ark *et al.*, 1978; Lambrechts *et al*, 1984, 1986; Lambrechts and Rasmussen, 1984; Sanger *et al.*, 1985). Relevant biological activity on these substances is not available. The pyrimidines are formed by condensation of N-formylamphetamine (the intermediate formed in the Leuckart reaction) with an additional molecule of formamide, followed by cyclization and aromatization. The other substances in Figure 6, which include for example, four pyridines and one pyridone, result from condensation of two molecules of the precursor phenylacetone with one molecule of formamide.

Another type of toxic response from illicitly manufactured drugs is acute lead poisoning reported in two users of illicit methamphetamine

Figure 6

Weakly Basic Synthetic Contaminants Present in Amphetamine Synthesized Using the Leuckart Procedure



(Alcott, *et al*; 1987). Lead poisoning is generally an uncommon medical condition in adults which is usually industrial in origin. Intoxication from a single exposure is uncommon. Methamphetamine that was illicitly manufactured and injected was shown to be contaminated with lead (889 parts per million). The source of the lead was attributed to the reaction of lead acetate and phenylacetic acid to form the precursor, phenylacetone, as shown in Figure 7, which upon subsequent reaction with methylamine yields methamphetamine containing lead. Only seven cases of

Figure 7

Acute Lead Poisoning in Two Users of Illicit Methamphetamine

(Ref.: Alcott *et al.*, 1987)

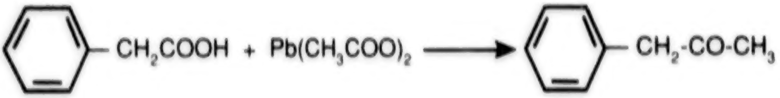
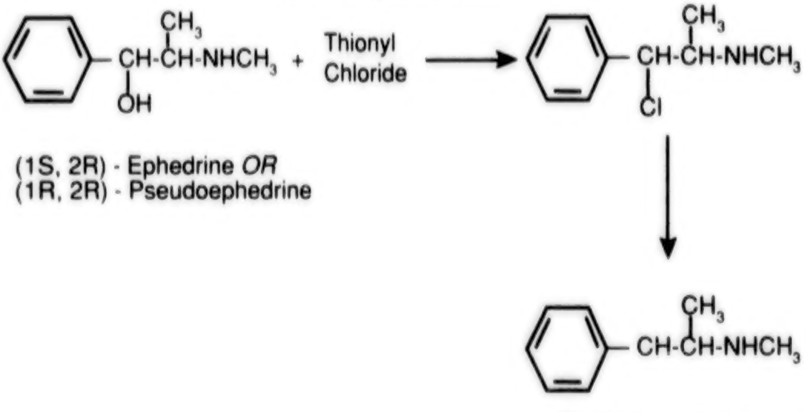


Figure 8

Synthesis of Methamphetamine From Ephedrine

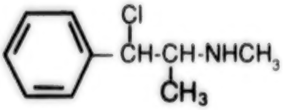


(1S, 2R) - Ephedrine *OR*
(1R, 2R) - Pseudoephedrine

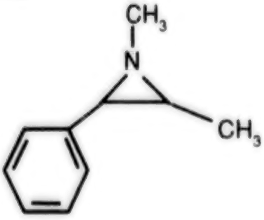
(R) -Methamphetamine

Figure 9

Two Impurities in Methamphetamine Produced From Ephedrine



Chloropseudoephedrine



1, 2-Dimethyl-3-Phenylaziridine

acute lead poisoning from intravenous exposure have been reported and these cases resulted from the intravenous injection of lead acetate-opium tablets dissolved in water. Early in 1987, a report of lead intoxication resulting from contaminated heroin was reported, although the source of the lead was not determined. (Parras *et al.*, 1987).

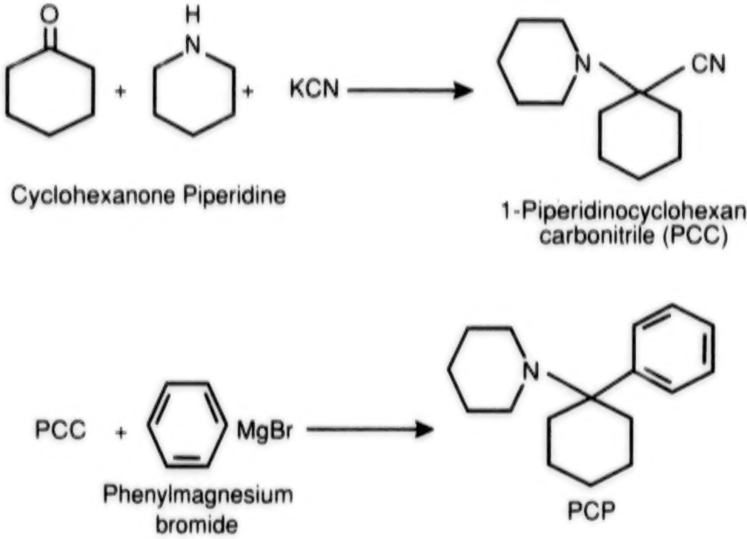
Another process commonly used for the illicit manufacture of methamphetamine in the United States and elsewhere involves ephedrine or pseudoephedrine as precursors. Most methods for methamphetamine synthesis involve the formation of a carbon-nitrogen bond and production of a racemic mixture, that is, equimolar amounts of the more potent S (dextrorotatory) isomer and the less potent R (levorotatory) isomer. The methamphetamine produced from the respective precursors, ephedrine or pseudoephedrine, would be expected to possess the same absolute configuration at the C–2 position since that position does not undergo any chemical reaction (Figure 8). A single enantiomer is obtained from each precursor. The resultant product of this procedure, that is, the S enantiomer of methamphetamine from (−)-ephedrine is a more potent stimulant than the racemic product derived from the reaction of phenylacetone and methylamine (the Leuckart reaction) (Noggle *et al;* 1986). Also, two additional impurities have been reported in clandestine methamphetamine which is formed by this process. Shown in Figure 9, one is the intermediate chloropseudoephedrine and the other is 1,2-dimethyl-3-phenylaziridine, formed by loss of the chlorine and by internal cyclization (Allen and Kiser, 1987). Although no pharmacologic data on the latter substance is available, the parent compound, aziridine, is considered extremely toxic, producing tissue necrosis, respiratory tract irritation and inflammation and a variety of blood disorders (Gosselin *et al.*, 1984).

Phencyclidine

The synthesis of phencyclidine (PCP) from piperidine, cyclohexanone and potassium cyanide, giving rise to the intermediate, 1-piperidinocyclohexanecarbonitrile (PCC), is described in Dr. Scaplehorn's paper and is shown in Figure 10 (Shulgin and MacLean, 1976; Soine, 1986). The precursors, piperidine and cyclohexanone, are relatively harmless solvents, especially relative to PCP itself (Gosselin *et al.*, 1984). However, the intermediate PCC has been described as even more toxic than PCP; PCC decomposes in physiologic saline giving rise to hydrocyanic acid (HCN) (Soine *et al.*, 1979, 1980). Additionally, when PCC is burned (that is, smoked in PCP-impregnated marijuana cigarettes), approximately 58 percent of the PCC breaks down to form cyanide and organic by-products; approximately 40 percent of the PCC remains intact with smoke (Lue *et al.*, 1988). The extent of occurrence of PCC in illicit PCP has been reported by several authors (Bailey *et al.*, 1976; Baker, 1982; Ballinger and Marshman, 1979; Cone *et al.*, 1980; Davis *et al.*, 1980; Dulik and Soine, 1981, Helisten and Shulgin, 1976; Soine *et al.*, 1980). In

Figure 10

Synthesis of Phencyclidine (PCP)



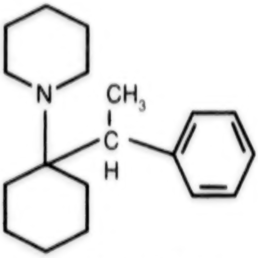
one laboratory, PCC was found in approximately twenty percent of the PCP samples examined (Ballinger and Marshman, 1979).

The quantity of PCC (as the hydrochloride salt) present in a dosage unit of PCP ranged from 0.01 to 0.28 milligram. The median quantity of PCP hydrochloride in tablets was 3.9 milligrams (range: 1.0 to 29.4 milligrams) and in capsules 3.1 milligrams (range: 0.001 to 142 milligrams). Another study on the contamination of illicit PCP with PCC revealed that one-third of seized powders, tablets, and green plant material containing PCP also contained the synthetic contaminant PCC (Soine *et al.*, 1980). The mole percent of PCC to PCP ranged from one to sixty-eight percent. As PCC is considered unstable, decomposing to HCN, piperidine and cyclohexanone, its analysis is difficult and its presence therefore may actually be greater than what is measured (Baker, 1982).

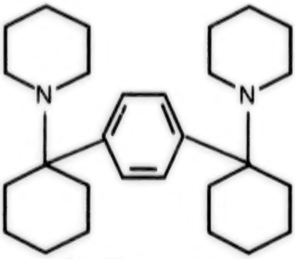
Analogues of PCP (1-(1-phenylcyclohexyl) pyrrolidine (PCPy) and 1-(1-phenylcyclohexyl)morpholine (PCM)) and analogous carbonitrile precursors (1-pyrrolidinocyclohexanecarbonitrile (PyCC) and 1-morpholinocyclohexanecarbonitrile (MCC)) were made and compared to PCP and PCC (Cone *et al.*, 1980). Acute lethal dose determinations of carbonitrile precursors and the respective phenylcyclohexyl derivatives of piperidine (PCP), pyrrolidine (PCPy) and morpholine (PCM) were conducted in mice. The LD–50's of the carbonitrile precursors, PCC, PyCC and MCC, ranged from 155 to 193 micromoles per kilogram, whereas those for PCP, PCPy and PCM were somewhat higher and ranged from 206 to 1,520 micromoles per kilogram.

Figure 11

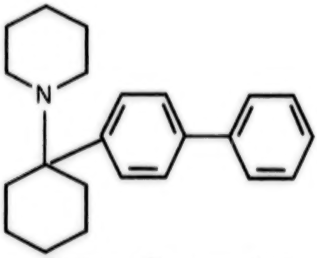
The Chemical Structures of Three Phencyclidine Co-Synthetics



Ethyl-Phencyclidine



Bis-Phencyclidine



Biphenyl-Phencyclidine

Toxicities for the precursors were almost equivalent—with MCC differing slightly from the other two precursors: 193 micromole/kg (MCC), 155 micromole/kg (PCC), and 162 micromole/kg (PyCC). However, within the final drug products there were significant differences in toxicity, with the low toxicity of PCM being particularly apparent (1,520 micromole/kg versus 283 micromole/kg for PCP and 206 micromole/kg for PCPy). Each carbonitrile precursor was more toxic in the mouse than was its corresponding parent phenylcyclohexyl compound. Thus, the contamination of illicit street samples by the more toxic carbonitrile precursor could increase the probability of an adverse reaction or a fatal overdose. The possibility of toxic synergism upon human exposure to PCC-contaminated street PCP was proposed.

The effects of three other by-products of PCP manufacture were studied to determine if they have pharmacological effects similar to PCP (Leander *et al.,* 1981). The substances, shown in Figure 11, are 1-[1-(4-biphenylyl)-cyclohexyl]-piperidine (biphenyl-PCP), 1,4-bis(1-cyclohexylpiperidine)benzene (bis-PCP), and [1-phenyl-1-(1-piperidino)]-ethane (ethyl-PCP). The substances exhibited different pharmacological effects than PCP, based upon response and discrimination studies in birds. Biphenyl-PCP was not PCP-like; additionally, with doses up to 1,000 mg/kg no toxicity or PCP like effects were observed. Ethyl-PCP at moderate to moderately high doses did not effect behavior, although the 500 mg/kg dose killed 80 percent of the subjects without exhibiting any PCP-like effects. The bis-PCP was the most toxic, killing pigeons at 20-40 mg/kg and quail at doses as low as 80 mg/kg. Some surviving birds exhibited behavioral abnormalities for at least 48 hours. The toxic effects of the bis-PCP may be additive with (or potentiated by) pure PCP.

Methaqualone

The synthesis of methaqualone from anthranilic acid (*ortho*-aminobenzoic acid), acetic anhydride, N-acetylanthranilic acid (*ortho*-acetamidobenzoic acid), *ortho*-toluidine (*ortho*-methylaniline), and catalysts is shown in Figure 12 (Soine, 1986; Ozaki *et al*; 1985). The methaqualone analogue, mecloqualone, arising from substitution of *ortho*-toluidine by *ortho*-chloroaniline is indicated as well. Figure 13 shows some of the impurities which have been found in clandestinely synthesized methaqualone (Angelos and Meyers, 1985). These include three precursors—anthranilic acid, N-acetylanthranilic acid and *ortho*-toluidine. *Ortho*-methylacetanilide results from acetylation of *ortho*-toluidine and 2-methyl-3-*o*-carboxyphenyl-4(3H)-quinazolinone results from the reaction of two molecules of N-acetylanthranilic acid. The major known problem resulting from methaqualone impurities involves *ortho*-toluidine which has been found to cause cancer of the bladder in several test animals. Additionally, *ortho*-toluidine has been reported to precipitate necrotizing cystitis—urinary bleeding with severe inflammation and ulceration throughout the bladder (Goldfarb and Finelli, 1974).

Figure 12

Synthesis of Methaqualone (R=CH_3) and Mecloqualone (R=Cl)

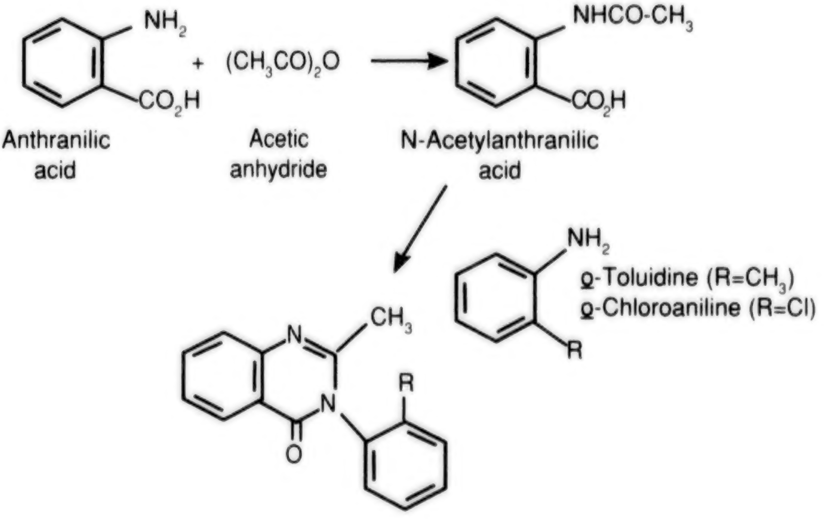
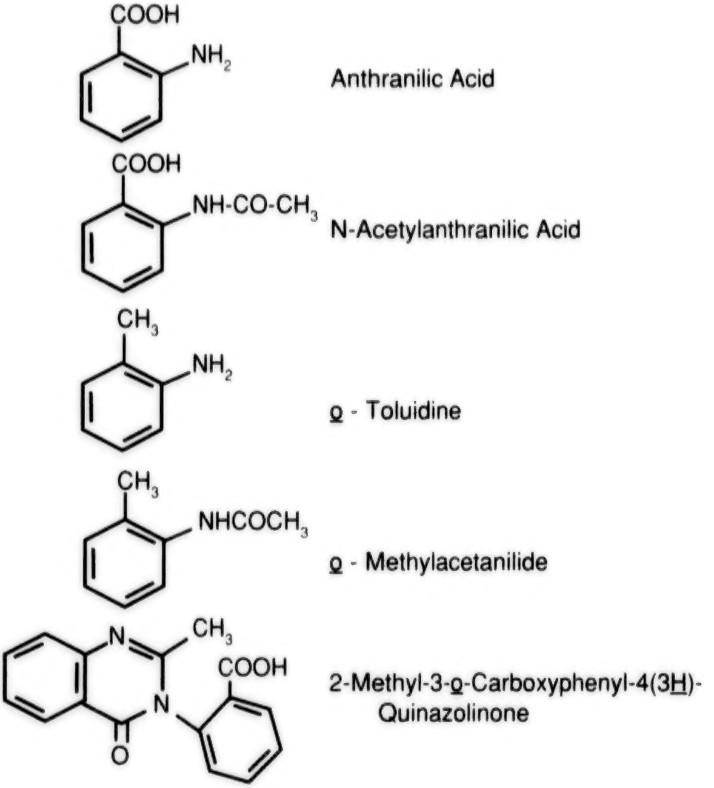


Figure 13
Methaqualone Impurities



Summary

As a chemical reaction proceeds, various impurities accumulate. These are: reactants, by-products, intermediates and contaminants within reagents. Specific impurities described were formic acid, alpha-benzylphenethylamines, N-formylamphetamine, pyrimidines, and pyridines in the amphetamines, enantiomerically pure and racemic methamphetamine; lead-contaminated methamphetamine and heroin; chloropseudoephedrine and 1,2-dimethyl-3-phenyl-aziridine in methamphetamine; the cycloalkylcarbonitrile intermediates in phencyclidine (PCP), the pyrrolidine analogue of PCP, and the morpholine analogue of PCP; *Ortho*-toluidine, anthranilic acid, N-acetylanthranilic acid, *ortho*-methylacetanilide and 2-methyl-3-O-carboxyhenyl-4(3H)-quinazolinone in methaqualone; processing solvents in cocaine, and numerous acetylation products of opiate alkaloids present in illicit heroin.

Only a limited amount of pharmacological or toxicological data exists for many of the impurities in these drugs. Much of the toxicological data that is currently available in the literature relates to prototypes of a chemical class and not to the specific entity found in the drug sample. Taking into consideration the possible presence of impurities in illicit drugs and their pharmacological and toxicological profiles, improved treatment of the drug abuser may be possible.

References

Alcott, J.V., III, R.A. Barnhart and L.A. Mooney, "Acute lead poisoning in two users of illicit methamphetamine" *JAMA, 258*(4), 510–511, 1987.

Allen, A.C. and W.O. Kiser, "Methamphetamine from ephedrine: 1. Chloroephedrines and aziridines," *J. Forens, Sci., 32*(4), 953–962, 1987.

Allen, A.C., D.A. Cooper, J.M. Moore, M. Gloger and H. Neumann, "Illicit heroin manufacturing byproducts: Capillary gas chromatographic determination and structural elucidation of narcotine- and norlaudanosine-related compounds," *Anal. Chem., 56*: 2940–2947, 1984.

Angelos, S.A. and J.A. Meyers "The isolation and identification of precursors and reaction products in the clandestine manufacture of methaqualone and mecloqualone," *J. Forens. Sci., 30*(4): 1022–1047, 1985.

Bailey, K., A.Y.K. Chow, R.H. Downie, and R.K. Pike, "1-Piperidinocyclohexanecarbonitrile, a toxic precursor of phencyclidine," *J. Pharm. Pharmac. Communications, 28*: 713–714, 1976.

Baker, J.K., "Detection of 1-piperidinocyclohexanecarbonitrile in illicit phencyclidine samples," *Anal. Chem. 54*: 347–349, 1982.

Ballinger, J.R. and J.A. Marshman "GLC quantitation of 1-piperidinocyclohexanecarbonitrile (PCC) in illicit phencyclidine (PCP)," *J. Anal. Toxicol., 3*: 158–161, 1979.

Barron, R.P., A.V. Kruegel, J.M. Moore, and T.C. Kram, "Identification of impurities in illicit methamphetamine samples," *J. AOAC, 57*(5): 1147–1158, 1974.

Boon, N.A., "Solvent abuse and the heart," *Brit. Med. J., 294*: 722, 1987.

Burns, Stanley R., "Effects of MPTP, an impurity in the synthesis of MPPP," presented at the WHO/DEA, USA Meeting on Technical Aspects of Drug Control (MNH/PAD/87.13—World Health Organization, Geneva), in Rabat, Morocco, 1987.

Cadet, J.L., C.R. Clark and S. Fahn, Behavioral effects of alpha-benzyl-N-methylphenethylamine (ABNMP), a methamphetamine analog: Inhibition by ketanserin and para-chlorophenylamine (PCPA), *Pharmacol, Biochem. Behav.*, 125–128, 1988.

Cone, E.J., D.B. Vaupel, and W.F. Buchwald, "Phencyclidine: detection and measurement of toxic precursors and analogs in illicit samples," *J. Anal. Toxicol., 4:* 119–123, 1980.

Dahab, G.M., S.E. Gerges, and M.S. Abdel-Rahman, "Effect of benzyl chloride on rat liver functions," *J. Toxicol. Envir. Health, 18,* 431–439, 1986.

Davis, G.C., A.C. Williams, S.P. Markey, H.M. Ebert, E.D. Cane, C.M. Reichert, and I.J. Kopin. "Chronic parkinsonism secondary to intravenous injection of meperidine analogues,' *Psych. Res., 1,* 249–254, 1979.

Davis, W.M., R.F. Borne, R.B. Hackett, and I.W. Walters, "Lethal synergism of phencyclidine with a precursor and contaminant, 1-piperidinocyclohexanecarbonitrile (PCC) in illicit phencyclidine, *Clin. Tox.,* 18(6), 737–742, 1981.

Fellman, J.H. and J.N. Nutt, "MPTP-like molecules and Parkinsons disease," *Lancet,* 924, 1985.

Goldfarb, M. and R. Finelli, "Necrotizing cystitis-secondary to 'bootleg' methaqualone," *Urology, 3*: 54–55, 1974.

Gosselin, R.E., R.P. Smith and H.C. Hodge, Editors, *Clinical Toxicology of Commercial Products,* Fifth Edition, Williams & Wilkins, Baltimore/London, 1984.

Helisten, C. and A.T. Shulgin, "The detection of 1-piperidinocyclohexanecarbonitrile contamination in illicit preparations of 1-(1-phenylcyclohexyl)-piperidine and 1-[1-(2-thienyl)-cyclohexyl]piperidine," *J. Chromatogr., 117,* 232–235: 1976.

Klein, M., "Analysis of impurities in illicit heroin by mass spectrometry," in *Mass Spectrometry in Drug Metabolism,* A. Frigerio and E.L. Ghisalberti, Editors, Plenum, New York, 449–463, 1977.

Kram, T.C., "Reidentification of a major impurity in illicit amphetamine," *J. Forens. Sci.,* 596–599, 1979.

Kram, T.C., and A.V. Kruegel, "The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy," *J. Forens. Sci.,* 22:40–52, 1976.

Lambrechts, M., T. Klemetsrud, K.E. Rasmussen and H.J. Storesund, "Analysis of Leuckart-specific impurities in amphetamine and methamphetamine," *J. Chromatogr.,* 284:499–502, 1984.

Lambrechts, M., and K.E. Rasmussen, "Analysis of impurities in illicit amphetamine by high-performance liquid chromatography," *J. Chromatogr.,* 295:264–268, 1984.

Lambrechts, M., and K.E. Rasmussen, "Leuckart-specific impurities in amphetamine and methamphetamine seized in Norway," *Bull. Narc.,* 36:47–57, 1984.

Lambrechts, M., F. Tonnesen and K.E. Rasmussen, "Profiling of impurities in illicit amphetamine samples by high-performance liquid chromatography using column switching," *J. Chromatogr.,* 369:365–377, 1986.

Langston, J.W., P. Ballard, J.W. Tetrud, and I. Irwin, "Chronic parkinsonism in humans due to a product of meperidine-analog synthesis," *Science,* 219:979–980, 1983.

Langston, J.W., E.B. Langston, and I. Irwin, "MPTP-induced parkinsonism in human and nonhuman primates—clinical and experimental aspects," *Acta Neurol. Scand.*, 70:49–54, 1984.

Lieberman, A.N., "Update on Parkinson disease," *N.Y. State J. Med.*, 147–153, 1987.

Lomonte, J.N., W.T. Lowry, and I.C. Stone, "Contaminants in illicit amphetamine preparations," *J. Forens. Sci.*, *21*: 575–582, 1976.

Lue, L.P., J.A. Scimeca, B.F. Thomas and B.R. Martin, "Pyrolyte fate of piperidinocyclohexanecarbonitrile, a contaminant of phencyclidine during smoking," *J. Anal. Toxicol.*, 12: 57–61, 1988.

Moore, J.M., A.C. Allen, and D.A. Cooper, "Determination of manufacturing impurities in heroin by capillary gas chromatography with electron capture detection after derivatization with heptafluorobutyric anhydride," *Anal. Chem.*, *56*: 642–646, 1984.

Nair, N.K., V. Navaratnam and V. Rajananda, "Analysis of illicit heroin I. An effective thin-layer chromatographic system for separating eight opiates and five adulterants," *J. Chromatogr.*, *366*: 363–372, 1986.

Noggle, F.T., C.R. Clark, T.W. Davenport, and S.T. Coker, "Synthesis, identification, and acute toxicity of α-benzyl-N-methylphenethylamine. Contaminants in clandestine preparation of amphetamine and methamphetamine," *J. AOAC*, *68*(6): 1213–1222, 1985.

Noggle, F.T., Jr., J. DeRuiter and C.R. Clark, "Liquid chromatographic determination of the enantiomeric composition of methamphetamine prepared from ephedrine and pseudoephedrine," *Anal. Chem.*, *58*: 1643–1648, 1986.

Ozaki, K., Y. Yamada, T. Oine, T. Ishizuka and Y. Iwasawa, "Studies on 4(1H)-Quinazolinones. 5. Synthesis and anti-inflammatory activity of 4(1H)-quinazoline derivatives," *J. Med. Chem.*, *28*: 568–576, 1985.

Parras, F., J.L. Patier and C. Ezpleta, "Lead-contaminated heroin as a source of inorganic-lead intoxication," *New Engl. J. Med.*, *316*(2): 755, 1987.

Sanger, D.G., I.J. Humphreys, A.C. Patel, M. Japp, and R.G.L. Osborne, "The significance of gas chromatographic impurity patterns obtained from illicitly produced amphetamine," *For. Sci. Internat.*, *28*: 7–17, 1985.

Shih, M.C. and S.P. Markey, "Quantification of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenylpyridinium ion in brain tissue by gas chromatography/mass spectrometry," *Biomed. Environ. Mass Spectrom.*, *13*: 85–89, 1986.

Shulgin, A.T., and D.E. MacLean, "Illicit synthesis of phencyclidine (PCP) and several of its analogs," *Clin. Tox.*, *9*(4): 553–560, 1976.

Sinnema, A. and A.M.A. Verweij, "Impurities in illicit amphetamine: a review," *Bull. Narc.*, *33*(3): 37–54, 1981.

Skowronski, G. and M.S. Abdel-Rahman, "Teratogenicity of benzyl chloride in the rat," *J. Toxicol. Environ. Health*, *17*: 51–56, 1986.

Soine, W.H., K.T. Brady, R.L. Balster, and J.Q. Underwood III, "Chemical and behavorial studies of 1-piperidinocyclohexanecarbonitrile (PCC): evidence for cyanide as the toxic component," *Res. Commun. Chem. Path. Pharmac., 30*(1): 59–70, 1980.

Soine, W.H., W.C. Vincek, D.T. Agee, J. Boni, G.C. Burleigh, T.H. Casey, M. Christian, A. Jones, D.T. King, D. Martin, D.J. O'Neil, P.E. Quinn, and P. Strother, "Contamination of illicit phencyclidine with 1-piperidinocyclohexanecarbonitrile," *J. Anal. Toxicol., 4*: 217–221, 1980.

Soine, W.H., "Clandestine drug synthesis," in *Medical Research Reviews, 6*(1): 41–74, John Wiley & Sons, Inc., 1986.

Strömberg, L., "Comparative gas chromatographic analysis of narcotics II. Amphetamine sulphate," *J. Chromatogr., 106*: 335–342, 1975.

Strömberg, L. and H. Bergkvist, "Comparative gas chromatographic analysis of narcotics IV. Methamphetamine hydrochloride," *J. Chromatogr., 258:* 65–72, 1983.

Strömberg, L. and A.C. Maehly, "Advances in chemical signature analyses of drugs," in *Instrumental Applications in Forensic Drug Chemistry,* eds. M. Klein, A.V. Kruegel and S.P. Sobol, Editors, Washington, D.C., U.S. G.P.O., 202–209, 1979.

Van der Ark, A.M., A.M.A. Verweij, and A. Sinnema, "Weakly basic impurities in illicit amphetamine," *J. Forens. Sci.,* 693–700, 1978.

Williams A., "MPTP parkinsonism," *Brit. Med. J., 289*: 1401–1402, 1984.

Wright, J.M., R.A. Wall, T.L. Perry, and D.W. Paty, "Chronic parkinsonism secondary to intranasal administration of a product of meperidine-analogue synthesis," *New Engl. J. Medicine, 310*(5): 325, 1984.

BLANK PAGE

The Methylenedioxy Amphetamines: Pharmacological, Behavioral and Neurotoxic Effects

Kevin T. Finnegan, M.D., Ph.D., and Charles R. Schuster, Ph.D.

Introduction

The phenylisopropylamines form a large and well-studied class of compounds. Structurally, the members of this class resemble the catecholaminergic neurotransmitters, dopamine and norepinephrine. It should come as no surprise then that a number of the agents belonging to this group are capable of exerting profound effects on central nervous system (CNS) function in both man and animals.

The biochemical and behavioral effects of the prototypical phenylisopropylamines, amphetamine and its N-methyl derivative, methamphetamine, have been the subject of considerable research attention. Both compounds are potent central and peripheral indirect-acting sympathomimetic agents, and the ability of these compounds to augment activity, brighten mood, enhance alertness, and decrease fatigue have been well described (Gunne, 1977). As a consequence of these properties, the last three decades have seen the development of several large-scale epidemics of amphetamine and related analogue abuse in the United States, Sweden, and Japan (Griffith, 1966; Jonsson and Gunne, 1970; Buening and Gibb, 1974).

Prompted by the appearance of these epidemics, investigators during the last 10 years have turned their attention to assessing the long-term neurochemical and behavioral effects of the amphetamines in experimental animals. An important observation arising from these efforts was the finding that the multiple dose administration of methamphetamine causes a persistent depletion of dopamine and serotonin in several regions of animal brain (Seiden *et al.*, 1975; Finnegan *et al.*, 1982; Wagner *et al.*, 1980). In rodents, the depletion of dopamine appeared to be related to the ability of methamphetamine to cause nerve terminal degeneration (Ricaurte *et al.*, 1982). Despite the presence of this neurochemical deficit, overt behavior in methamphetamine-treated primates appeared to be entirely normal when tested several weeks after completion of the repeated dosing regimen (Fischman and Schuster, 1977; Finnegan *et al.*, 1982), perhaps reflecting the operation of compensatory mechanisms. While methamphetamine-treated animals displayed no overt behavioral disturbance, however, they clearly showed an altered sensitivity to various drugs thought to exert their effects through central dopaminergic systems (Finnegan *et al.*, 1982; Lucot *et al.*, 1980).

The long-term neurochemical and behavioral consequences resulting from chronic amphetamine administration have recently been reviewed (Seiden and Ricaurte, 1987). We will therefore focus on more recent research concerning the behavioral, pharmacological, and neurotoxic effects of several popularly abused ring-substituted amphetamines, specifically the methylenedioxy analogues.

The Methylenedioxy Ring-Substituted Amphetamines

Background

The phenethylamine structure permits a great number of substitutions, with about 2,000 derivatives having been synthesized and characterized (Richards, 1972). Approximately 30 of these analogues have been evaluated in humans (Shulgin, 1970). Several have found their way into the illicit drug market, where they have become known on the street as MDA (3,4-methylenedioxyamphetamine), MDMA (3,4-methylenedioxymethamphetamine), MMDA (3-methoxy-4,5-methylenedioxyamphetamine), DOM (4-methyl-2,5-dimethoxyamphetamine), and DOB (4-bromo-2,5-dimethoxyamphetamine). The abuse of MDA and MDMA, in particular, has become widespread. MDMA is currently one of the most popularly abused drugs in the United States (Beck, 1986; Adler *et al.*, 1985). Recently, a third analogue in this series, MDE (3,4-methylenedioxyethylamphetamine), has been identified in street samples of confiscated material (Vallejo, personal communication). A concerted effort to explore the properties and actions of the methylenedioxyamphetamines has only recently been undertaken, and much remains to be learned. Although incomplete, the available evidence indicates that MDA, MDMA, and MDE exert similar psychotropic effects in man and animals. Hence, these three agents will be discussed together as a class. Differences between the three compounds will be pointed out where data is available.

MDA and MDMA were actually synthesized in the early part of this century (Mannich and Jacobsohn, 1910). Patented in the early 1960's as anorectic agents, the drugs were never marketed due to their marked psychoactive properties. MDA became popular as a drug of abuse during the 1960's (Ratcliffe, 1974). With the classification of MDA as a Schedule I compound under the U.S. Controlled Substances Act in 1970, MDMA surfaced on the illicit drug market during the 1970's as an unscheduled substitute. Because of the increased illicit use of MDMA, and the lack of detailed laboratory studies, the U.S. Drug Enforcement Administration classified MDMA in 1985 as a Schedule I compound. Legislation regarding the classification of MDE, the newest "designer drug" in this series, is pending (Sapienza, personal communication). Although both MDA and MDMA have been advocated as therapeutic adjuncts to psychotherapy (Ratcliffe, 1974; Grinspoon and Bakalar, 1986), no controlled trials to document and investigate their clinical effects have yet been reported. MDMA is said to be safe by psychotherapists and users

(Baum, 1985; Gehlert *et al.*, 1985), but recently the compound has been implicated as a cause of death in 5 individuals (Dowling *et al.*, 1987). Experience with MDE is as yet limited, but anecdotal reports suggest that this analogue possesses an abuse liability similar to that of MDMA (Sapienza, personal communication).

Behavioral Effects

The substitution of the methylenedioxy function on the ring of amphetamine or methamphetamine converts the parent compounds, which are potent CNS stimulants, into agents that possess psychedelic properties as well. Subjectively, users of MDA report an intensification of feelings, increased self-insight, and aesthetic enjoyment (Shulgin, 1978). It is said that individuals under the influence of this drug tend to focus on the nature of interpersonal relationships, and display an overwhelming desire to be with and talk to other people (Ratcliffe, 1974). The MDA experience is usually devoid of hallucinations, perceptual distortions, or closed-eye imagery, all of which are common reactions to LSD, mescaline, or psilocybin. In keeping with the close structural similarity of MDA to amphetamine, the subjective effects in humans are also characterized by a stimulatory component (Yensen *et al.*, 1976).

Similar to MDA, the intoxication induced by MDMA is reportedly characterized by euphoria, increased sensory awareness, and mild central stimulation (Adler *et al.*, 1985). Different from MDA, MDMA has a shorter duration of action and less hallucinogenic character (Anderson *et al.*, 1978; Shulgin and Nichols, 1978). The analogue MDE has only recently been identified in samples of confiscated drug, and information regarding its psychopharmacological effects is scanty. The drug is reported to induce a subjective state similar to MDA or MDMA, but its effects occur more rapidly following ingestion and are shorter-lived (Shulgin, 1978).

Evidence derived from behavioral investigations in animals suggests that MDA and MDMA produce both hallucinogenic and amphetamine-like effects. The administration of MDA and MDMA to pigeons (Evans and Johanson, 1986) or monkeys (Kamien *et al.*, 1986) trained to discriminate amphetamine from saline results in responding on the amphetamine appropriate lever. Glennon and Young (1984) demonstrated that in rats trained to discriminate MDA from saline, certain doses of either amphetamine or the hallucinogenic ring-substituted amphetamine, DOM, produce MDA appropriate responding. In animals trained to discriminate DOM from saline, stimulus generalization occurs upon administration of MDA (Glennon *et al.*, 1982), but not amphetamine (Silverman and Ho, 1980). Therefore, MDA appears to produce discriminative cues in rats that are similar to those induced by either amphetamine or the hallucinogen, DOM. Interestingly, further work demonstrated that MDMA did not substitute for DOM in DOM-trained rats (Glennon, 1986), suggesting that the discriminative cues induced by MDMA may more closely resemble those of amphetamine than DOM.

Drug discrimination paradigms, such as those employed above, provide a way of modeling the human drug experience in animals (Woolverton and Schuster, 1983). Given the known abuse liability of amphetamine, the observation that amphetamine and the methylenedioxy-substituted analogues share, at least in part, similar stimulus properties has raised concerns about the abuse liability of the latter compounds. Recently, drug self-administration studies in primates have provided more direct evidence regarding the abuse liability of MDA and MDMA (Griffiths *et al.*, 1979; Beardsley *et al.*, 1986; Lamb and Griffiths, 1987). Monkeys trained to lever press for intravenous injections of cocaine continue to respond at rates significantly elevated above saline baseline when MDMA or MDA were substituted. Since drugs, abused by humans, are usually intravenously self-administered by primates (Johanson and Balster, 1978), these studies suggest that the methylenedioxy-substituted amphetamines may indeed possess significant potential for abuse.

Pharmacological Effects

Amphetamine analogues are known to produce a diversity of behavioral effects in animal models. In many cases, the various behavioral components or responses resemble those induced by amphetamine itself or, as in the case of the amphetamine analogue DOM, the hallucinogenic agent LSD. The central stimulant action of amphetamine appears related to the ability of this compound to release presynaptic stores of dopamine and norepinephrine, block their reuptake, and at high concentrations to inhibit the degradative enzyme, monoamine oxidase (Moore, 1978). The psychotropic actions of LSD, DOM, and other hallucinogens on the other hand, appear to depend on the ability of these compounds to interact with central serotonergic systems (Aghajanian, 1984). As discussed above, the behavioral evidence suggests that MDA and MDMA interact with both neurotransmitter systems. This idea is supported by data from pharmacological studies. For example, the administration of MDA or MDMA to rodents causes increased locomotor activity, grooming behavior, and piloerection, signs indicative of central sympathomimetic activity (Thiessen and Cook, 1973; Stone *et al.*, 1987). Overdose with MDA in humans is characterized by symptoms of peripheral and central sympathomimetic over-stimulation (Simpson and Rumack, 1981). Biochemically, MDMA and MDA have been shown to be potent releasers of dopamine in synaptosomal preparations (Schmidt, 1987) and, in addition, to inhibit the synaptosomal reuptake of dopamine and norepinephrine (Steele *et al.*, 1987). Hence, these biochemical actions may explain the capability of MDA and MDMA to augment sympathomimetic activity, as well as inducing amphetamine-like effects in various behavioral paradigms.

Related to the ability of these drugs to produce psychedelic effects in humans and hallucinogenic appropriate responding in animals, biochemical studies with MDMA have shown this compound to be a more potent releaser of serotonin than of dopamine (Schmidt, 1987). Further, MDMA is more effective than amphetamine in blocking the uptake of this indolamine (Steele *et al.,* 1987). These biochemical actions would be expected to increase concentrations of serotonin at synaptic sites in brain. Since alterations in serotonergic function have been implicated in the ability of hallucinogenic drugs to produce changes in perception (Jaffe, 1980) these data may explain the capacity of MDMA and MDA to produce psychedelic effects in humans.

Clearly, investigations directed at elucidating the pharmacological and behavioral effects of the methylenedioxyamphetamines are in their infancy. The available evidence suggests that MDA and MDMA possess a unique psychopharmacological spectrum of action that includes both stimulant and psychedelic properties. The question of whether such properties might prove useful therapeutically, however, remains to be addressed by appropriately designed clinical studies. In addition, any demonstrable clinical utility must be assessed in light of the increasing evidence that, in animals, these compounds are neurotoxic.

Neurotoxicological Effects

Two lines of evidence suggested that a study of the neurotoxic effects of the methylenedioxy-substituted amphetamines might prove worthwhile. The first set of data, discussed briefly above, indicated that methamphetamine induced a long-lasting decrease in the concentration of dopamine and serotonin in the brain of monkeys and rodents, accompanied by morphologic changes indicating nerve terminal degeneration (see Seiden and Ricaurte, 1987, for review). The toxic effects of methamphetamine occurred at relatively high doses of drug, doses 50 to 100 times higher than the amount required to produce behavioral changes. A second set of data showed that certain ring-substituted amphetamine derivatives, such as para-chloroamphetamine, produced a marked and persistent reduction in the concentration of CNS serotonin and its metabolites in animals (Fuller *et al.,* 1965; Sanders-Bush *et al.,* 1972). Further studies concluded that this persistent depletion of serotonin could be explained on the basis of para-chloroamphetamine's ability to damage serotonergic nerve fibers (Fuller, 1978).

MDA

Prompted by these observations, a number of investigators turned their attention to examining the long-term neurochemical consequences resulting from the administration of the methylenedioxy ring-substituted amphetamines. Ricaurte *et al.,* (1985) reported that MDA produced a long-lasting dose-related depletion of serotonin and its metabolite, 5-hydroxyindolacetic acid (5HIAA), in the striatum and hippocampus of rats two weeks after completion of a multiple dosing regimen (range: 5–40 mg/kg/dose, given twice each day for 4 days). Concentrations of dopamine and norepinephrine appeared unaffected. Uptake studies indicated that MDA-induced depletion of brain serotonin was accompanied by a loss of serotonergic uptake sites. Other work demonstrated persistent reductions in the ability of the serotonin synthesis enzyme, tryptophan hydroxylase, following MDA administration (Stone *et al.*, 1987). Morphologic studies (Fink–Heimer silver stain) revealed the presence of degenerating axonal terminals in the hippocampus of animals treated with MDA (Ricaurte *et al.*, 1985). Hence, the ability of MDA to cause a long-lasting decrease in the concentration of brain serotonin appears to be explained by its capacity to damage serotonergic neurons.

MDMA

Use of MDA crested in the late 1960's, but with the scheduling of the compound under the Controlled Substances Act in 1970 its popularity dropped considerably. Always one step ahead of the regulatory process, however, clandestine chemists soon began synthesizing its then unregulated N-methylated analogue, MDMA. Due to its current popularity, MDMA has recently become the object of considerable research attention. These studies have provided strong evidence indicating that MDMA, similar to MDA, damages serotonergic systems in rodent brain. For example, the multiple dose administration of MDMA to rats (dose range: 10 to 40 mg/kg/dose) produces a long-lasting depletion of serotonin and the metabolite 5HIAA in a variety of brain areas (Schmidt *et al.*, 1986; Stone *et al.*, 1987; Ricaurte *et al.*, 1987; Commins *et al.*, 1987). As was the case with MDA, this long-term depletion was found to be accompanied by a loss of serotonergic uptake sites (Schmidt, 1987; Commins *et al.*, 1987) as well as a reduction in the activity of tryptophan hydroxylase (Stone *et al.*, 1987).

Reports vary as to the ability of MDMA to induce persistent reductions of other neurotransmitters. Depending on the brain area examined, the dose, and time of sacrifice, concentrations of dopamine have been noted to be decreased (Commins *et al.*, 1987), increased (Schmidt *et al.*, 1986; Mokler *et al.*, 1987), or unaffected (Stone *et al.*, 1987). Levels of norepinephrine are reported to be decreased after high doses of MDMA (Commins *et al.*, 1987; Mokler *et al.*, 1987). Together, however, the available data indicate that serotonergic systems are by far the most sensitive to the persistent amine-depleting effects of MDMA.

Similar to MDA, morphologic studies revealed the presence of degenerating nerve terminals in the striatum of rats treated with relatively high doses of MDMA (80 mg/kg/dose, twice daily for 2 days) (Commins *et al.*, 1987). Hence, the MDMA-induced depletion of serotonin would appear to represent a true neurotoxic effect of the drug, rather than simply a long-lived pharmacological action, such as has been demonstrated for the drug reserpine. Interestingly, evidence of neuronal degeneration was also observed in a localized area of rat primary somatosensory cortex (layers III and IV). Here, actual degeneration of cell bodies was observed. This stands in contrast to the histologic changes observed in the striatum of MDMA-treated rats, in which only nerve terminal damage was evident (Commins *et al.*, 1987). The distinction is important because if cell bodies are irreparably damaged, regeneration is not possible. Regeneration of neurons can occur, on the other hand, if damage is limited to fiber terminals (Baumgarten *et al.*, 1973; Bjorklund *et al.*, 1973). We have recently found that serotonin levels in the hippocampus of rats treated with MDMA do in fact undergo a partial recovery with time (Finnegan *et al.*, 1987). These data suggest that, in the rat hippocampus at least, MDMA primarily damages the nerve terminal. Whether the partial recovery of serotonin represents regenerative sprouting of nerve fibers, accompanied by actual functional reinnervation, has yet to be determined. Further morphologic studies will be needed to clarify whether MDMA is capable of producing actual serotonergic cell loss.

It would seem unlikely that regeneration or recovery of function occurs in the somatosensory cortex, since MDMA does appear to produce cell loss in this area. The identity and function of these somatosensory neurons is unclear. Since neocortical neurons do not contain either indole (Azmitia, 1978) or catecholamines (Lindvall and Bjorklund, 1978), however, this finding indicates that MDMA may possess a broader spectrum of neuronal toxicity than originally thought. Whether similar morphologic changes occur in the somatosensory cortex after the administration of MDA has not been reported.

MDE

Finally, the neurotoxic potential of the newest "designer drug" to appear in this line, MDE, has also been recently addressed. Administration of this compound produces neurochemical changes similar to that induced by MDA and MDMA, that is, a long-lasting reduction in the concentration of serotonin and tryptophan hydroxylase activity in rat brain (Ricaurte *et al.*, 1987; Stone *et al.*, 1987). Lengthening the n-alkyl chain by one carbon, however, causes a reduction in potency. Compared to MDMA, approximately four-fold higher doses of this compound are required to produce long-term depletions of brain serotonin and reductions in tryptophan hydroxylase activity. Whether MDE is capable of damaging nerve terminals is unknown, but would seem likely given the similarity of this compound to MDA and MDMA.

Mechanisms of Toxicity

Studies focusing on how the methylenedioxyamphetamines damage neurons have only just begun. The available evidence suggests that it is unlikely that the toxic effects of these compounds appear as a consequence of a nonspecific reaction in the CNS, such as ischemia or the inhibition of protein synthesis. As discussed above, the drugs primarily affect serotonergic systems, leaving catecholaminergic neurons relatively unscathed. Moreover, the morphologic lesions induced by these drugs appear discrete (Ricaurte *et al.*, 1985; Commins *et al.*, 1987). Finally, the serotonergic depletions induced by MDMA can be blocked by the prior administration of serotonergic reuptake blockers (Schmidt, 1987).

Time course studies indicate that the effects of MDMA on serotonergic systems in rat brain can be temporally separated into two phases: An immediate effect and a delayed reaction (Schmidt, 1987). Both phases are manifested by depletions of serotonin. The immediate effect of MDMA is to cause a profound (greater than 80 percent) depletion of serotonin shortly after drug administration. This phase appears completely reversible, with neurotransmitter levels returning to control levels within 24 hours afterward. Following the initial recovery of serotonin, a second, non-reversible depletion of this amine then develops over a period of several days. These two actions can be separated pharmacologically and appear to be distinct. For example, the initial depletion of serotonin is produced by the administration of either the (+) or (−) MDMA isomers. In contrast, the non-reversible phase of depletion is solely the property of the (+) isomer. Moreover, the second, but not the first, depletion phase can be blocked by the prior administration of serotonergic reuptake blockers. Based on these differential effects, Schmidt (1987) suggests that the two phases of depletion may be mediated by separate mechanisms. In particular, the ability of reuptake inhibitors to block the non-reversible depletion of serotonin suggests that the generation of an endogenously produced toxic metabolite may be important.

Although the exact chain of events leading to neuronal damage has yet to be clarified, the mechanism of MDMA-induced toxicity appears to share certain common links with that caused by methamphetamine. Pretreatment with the gamma-aminobutyric acid (GABA) transaminase inhibitor, amino-oxyacetic acid, blocks the amine depletions caused by both methamphetamine (Hotchkiss and Gibb, 1980) and MDMA (Stone *et al.,* 1987). Similarly, inhibiting the synthesis of dopamine by administration of alpha-methylparatyrosine likewise prevents methamphetamine (Wagner *et al.,* 1983) and MDMA-induced (Gibb, personal communication) amine depletions. Moreover, the MDMA-induced morphologic changes observed in the striatum and somatosensory cortex are not unique to this agent, but have also been described after methamphetamine administration (see Seiden and Ricaurte, 1987). These converging data raise the possibility that the two drugs may, at least in part, share a common mechanism of action.

The Question of Toxicity in Humans

Whether MDA or MDMA produce neurotoxicity in humans has not been established, but is of obvious importance to the many individuals who use the drug for medicinal or abuse purposes. Clearly, the initial studies examining the effects of these compounds in animals employed conditions quite different from those under which humans typically ingest the drug. In rodents, the lowest effective dose of MDA or MDMA required to produce long-term neurochemical alterations is on the order of 5 to 10 mg/kg. This dose is approximately two to four times the behaviorally effective dose of the compounds in this species, and about three to five times higher than those used by humans (approximately 1.7 to 2.7 mg/kg, ingested orally) to produce cognitive changes.

In addition to dose, considerations regarding differences in drug sensitivity and metabolism, as well as the route and schedule of administration, have limited extrapolation of the findings in animals to humans. However, several recent studies have begun addressing these differences, bridging the gap between experimental investigations and human abuse patterns. For example, we have recently found that the neurotoxic effects of orally administered MDMA in rats are comparable to those observed after its subcutaneous injection (Finnegan *et al.,* 1987). Other investigators (Mokler *et al.,* 1987; Commins *et al.,* 1987) have demonstrated that single parenteral doses of MDMA are also effective in producing long-term depletions of serotonin in rat brain. In addition, persistent MDMA-induced depletions of serotonin have now been observed in primates (Ricaurte *et al.,* submitted), a species more closely related to humans. Importantly, the lowest effective dose of MDMA required to produce a long-term depletion of cortical serotonin in primates was 2.5 mg/kg. This dose is quite close to that ingested by humans, and obviously raises concerns regarding the drug's neurotoxic potential in man. Clinical studies addressing the question of whether individuals exposed to MDMA have decreased cerebrospinal levels of the serotonin metabolite, 5HIAA, or whether they display functional deficits attributable to serotonergic systems, will be needed to answer this important question.

Conclusions

A number of mental health specialists have advocated the use of MDA and MDMA as adjuncts in psychotherapy, and have opposed the placement of the latter compound in Schedule I of the Controlled Substances Act (Grinspoon and Bakalar, 1986). Evidence obtained in animals, however, strongly suggests that these drugs are capable of damaging serotonergic systems in brain. Moreover, recent studies indicate that these neurotoxic actions continue to be expressed under conditions which more closely parallel the pattern of use in humans. Until definitive clinical studies can be carried out, humans using these psychoactive drugs should be wary of their potential neurotoxic effects.

References

Adler, I., Abramson, P., Katz, S., Hager, M. *Newsweek,* 96 (April 15, 1985).

Aghajanian, G.K., In Hallucinogens; Neurochemical, Behavioral, and Clinical Perspectives, Jacob, B.S. (ed), Raven Press, NY, 171, 1984.

Anderson, G.M., Braun, G., Braun, U., Nichols D.E., and Shulgin, A.T. In: NIDA Res Mongr 22: 8, 1978.

Azmitia, E.C. In: Handbook of Psychopharmacology, Vol 9, Iverson, L.L., Iverson, S.D., and Snyder, S.H. (eds), Plenum Press, NY, 233, 1978.

Baum, R.M., *Chem, Eng. News,* 63: 7 (1985).

Baumgarten, H.G., Long-term recovery of serotonin after 5,6-dihydroxytryptamine, *Life Sci,* 12:357 (1973).

Beardsley, P.M., Balster, R.I. and Harris, L.S., *Alcohol Drug. Depend.,* 18: 149, (1986).

Beck, J. *Contemp. Drug Probl.,* 13: 23, (1986).

Bjorklund, A., Regeneration of central 5HT neurons after 5,6-dihydroxytryptamine, *Brain Res.,* 50:214 (1973).

Buening, M.K., Gibb, J.W., *Eur. J. Pharmacol.,* 26: 30 (1974).

Commins, D.L., Vosmer, G., Virus, R.M., Woolverton, W.L., Schuster, C.R., and Seiden, L.S., *J. Pharmacol. Exp. Ther.* 241: 338 (1987).

Dowling, G.P., McDonough, E.T. and Bost, R.O. *J. Am. Med. Assoc.,* 257: 1615 (1987).

Evans, S.M., and Johanson, C.E., *Drug Alchohol Depend.,* 18: 159 (1986).

Finnegan, K.T., Ricaurte, G.A., Ritchie, L.D., Irwin, I., Peroutka, S.J., and Langston, J.W., *Brain Res.,* in press (1988).

Finnegan, K.T., Ricaurte, G.A., Seiden, L.S., and Schuster, C.R., *Psychopharmacology* 77: 43 (1982).

Fischman, M.W., and Schuster, C.R., *J. Pharmacol. Exp. Ther.,* 201: 593 (1977).

Fuller, R.W., *Anna. N.Y. Acad. Sci.,* 305:178 (1978).

Fuller, R.W., Hines, C.W., and Mills, J., *Biochem. Pharmacol.,* 14: 483 (1965).

Gehlert, D.R., Schmidt, C.J., and Wu, L., *Eur. J. Pharmacol.,* 119: 135 (1985).

Glennon, R.A., *Drug Alcohol Depend.,* 17: 119 (1986).

Glennon, R.A. and Young, R., *Pharmacol. Biochem. Behav.,* 20: 301 (1984).

Glennon, R.A., Young, R., Rosencrans, A., and Anderson, G.M., *Biol. Psychiatr.* 17: 807 (1982).

Griffith, J., *Am. J. Psychiatry.,* 123: 560 (1966).

Griffiths, R.R. Brady, J.V., and Bradford, L.D., In: Advances in Behavioral Pharmacology, Vol 2, Thompson, T., Dews, P.B. (ed), Academic Press, New York, p. 163, 1979.

Grinspoon, L. and Bakalar, J., *Psychiatric Times,* 18, (April 5, 1986).

Gunne, L.M., In Drug Addiction II, Martin, W.R. (ed), Springer Verlag, NY, p. 248, 1977.

Hotchkiss, A.J. and Gibb, J.W., *J. Pharmacol. Exp. Ther.,* 214: 257 (1980).

Jaffe, J.H. and Martin, W.R., In The Pharmacological Basis of Therapeutics, Gilman, A.G., Goodman, L.S., and Gilman, A. (eds), MacMillan Co., NY, p. 494, 1980.

Johanson, C.E. and Balster, R.L., *Bull. Narc.,* 30: 43 (1978).

Jonsson, L. and Gunne, L., In Amphetamines and Related Compounds, Costa, E. and Garattini, S. (eds), Raven Press, NY, p. 929, 1970.

Kamien, J.B., Johanson, C.E., Schuster, C.R. and Woolverton, W.L., *Drug Alcohol Depend.,* 18: 139 (1986).

Lamb, R.J. and Griffiths, R.R., *Psychopharmacol.,* 91: 268 (1987).

Lindivall, O., and Bjorklund, A., In: Handbook of Psychopharmacology. Vol 9, Iverson, L.L., Iverson, S.D. and Snyder, S.H. (eds), Plennum Press, NY, p. 139, 1978.

Lucot, J. Wagner, G., Schuster, C.R., and Seiden, L.S., *Pharmacol. Biochem. Behav.* 13: 409 (1980).

Mannich, C. and Jacobsohn, W., *Berichte,* 43: 189 (1910).

Mokler, D.J. Robinson, S.E. and Rosecrans, J.A., *Eur. J. Pharmacol.,* 138: 265 (1987).

Moore, K.E., In Handbook of Psychopharmacology. Vol 11, Iversen, L. and Snyder, S. (eds), Plennum Press, NY, p. 41, 1978.

Rathcliffe, B.E., *Clinical Toxicol.,* 7: 409 (1974).

Ricaurte, G.A., Finnegan, K.F., Nichols, D.E., Delanney, L.E., Irwin, I. and Langston, J.W., *Eur. J. Pharmacol., 137*: 265 (1987).

Ricaurte, G.A., Bryan, G. Strauss, L. Seiden, L.S. and Schuster, C.R., *Science, 229*: 986. (1985).

Ricaurte, G.A., Guillery, R.W., Seiden, L.S., Schuster, C.R., and Moore, R.Y., *Brain Res., 235*: 93–103 (1982).

Richards, R.N., *Can. Med. Assoc., 106*: 256 (1972).

Sanders-Bush, E., Bushing, J.A. and Sulser, F., *Eur. J. Pharmacol, 20*: 35 (1972).

Schmidt, C.J., *J. Pharmacol. Exp. Ther., 240*: 1 (1987).

Schmidt, C.J., *Eur. J. Pharmacol., 136*: 81 (1987).

Schmidt, C.J., Wu, L. and Lovenberg, W., *Eur. J. Pharmacol., 124*: 175 (1986).

Schuster, C.R. and Balster, R.L. *Adv. Behav. Pharmacol, 1*: 85 (1977).

Seiden, L.S. and Ricaurte, G.A., In Psychopharmacology: A Third Generations of Progres, Meltzer, H.Y. (ed), Raven Press, NY, p. 359, 1987.

Seiden, L.S., Fischman, M.W. and Schuster, C.R., *Drug Alcohol Depend., 1*: 215 (1975/76).

Shulgin, A.T., In Handbook of Psychopharamcology. Vol 11, Iverson, L.L., Iversen, S.D. and Snyder, S.H. (eds), Plennum Press, NY, p. 243, 1978.

Shulgin, A.T. and Nichols, D.E., In The Psychopharmacology of Hallucinogens, Stillman, R. and Willette, R. (eds), Perganmon Press, NY, p. 741, 1978.

Silverman, P.B. and Ho, B.T., *Psychopharmacol. (Berlin),* 68: 209 (1980).

Simpson, D.L. and Rumack, B.H., *Arch. Intern. Med.,* 141: 1507. (1981).

Steele, T.D., Nichols, D.E. and Yim, G.K., *Biochem, Pharmacol.,* 36: 2297 (1987).

Stone, D.M., Hanson, G.R. and Gibb, J.W., *Soc. Neurosci. Abstr.* 13(2): 904 (1987).

Stone, D.M., Johnson, M, Hanson, G.R. and Gibb, J.W., *Eur, J. Pharmacol.,* 134: 245 (1987).

Thiessen, P.N. and Cook, D.A., *Clin. Toxicology,* 6: 193 (1973).

Wagner, G.C. Ricaurte, G.A., Johanson, C.E, and Schuster, C.R., *Neurology,* 30: 547 (1980).

Wagner, G.C., Lucot, J.B., Schuster, C.R. and Seiden, L.S., *Brain Res.*, 270: 285 (1983).

Woolverton, W.L. and Schuster, C.R., *Pharmacol. Rev.*, 35: 33 (1983).

Yensen, R., Dileo, F., Lead, J.R., Richards, W. *et al.*, *J. Nerv. Ment. Dis.*, 163: 233 (1976).

Organ Toxicity

S.D. Ferrara, M.D. and L. Cima

Introduction

Drugs of abuse may inflict many damaging effects on various functional and organ systems as a result of their repeated administration. In addition, they may induce drug-seeking behavior and cause tolerance and dependence.

Psychoactive drugs are apt to produce complications on central-autonomic nervous, cardiovascular, immune and reproductive systems, liver and kidney. Physiopathological mechanisms, drug interactions, effect, and mortality related to various functional and organ systems are treated with specific reference to synthetically produced substances.

Physiopathological Mechanisms

The *central nervous system* (CNS) is protected from toxicants by the blood-brain barrier. The "barrier" is a functional concept based on observations that some substances that enter and affect many of the soft tissues of the body, such as liver, kidney, and muscle, are excluded from the brain. Not all substances are preferentially excluded from the brain: for example, most psychoactive drugs, anesthetics, analgesics, and tranquilizers penetrate the blood-brain barrier, while highly polar compounds tend to be excluded. In the immature brain, the barrier is generally not as effective, and toxic doses of some compounds, such as inorganic salts, may accumulate in the CNS of children, while the adult develops marked effects on the peripheral nervous system instead. Because of specificity of this kind in regard to uptake of substances in the brain, there is a considerable amount of research and speculation regarding the anatomic features that relate to the functional barrier (Davies, 1985). When cells are damaged by exposure to toxic chemicals either by direct contact with the chemical or by secondary effects such as anoxia subsequent to diminished oxygen supply, some similar effects are observed. These effects are swelling of the cell and cytoplasmic organelles, dispersion of the rough endoplasmic reticulum (RER), and swelling of the nucleolus. The changes are accompanied by decreases in cytoplasmic pH, in the activity of oxidative enzyme systems, and in the synthesis of protein and other cell components. Differences in response relate more to quantitative differences in amount and rate of change in organelles of different cell types than to qualitative differences. Thus, cells with little capacity for anaerobic metabolism but with rapid ionic shifts through the external membrane, such as myocardial cells and neurons, are susceptible during anoxia to rapid edema from the loss of integrity of the cell membrane.

On the other hand, liver cells will first show changes in the endoplasmic reticulum, diminished protein synthesis, and lipid accumulation. However, both the electrically excitable cells and liver cells will show both types of injury responses over a period of hours.

The neuron is a cell that has little capacity for anaerobic metabolism and a high metabolic rate. The oxygen consumption of neurons is ten times higher than the oxygen consumption of glial cells. This combination of metabolic conditions puts the neuron at more risk from anoxia than glial cells.

Neuronal damage starts within a few minutes after cessation of blood flow to the brain, and death of some neurons occurs before complete cessation of oxygen or glucose transport. Certain cells are more sensitive to anoxia than others. The sequence of vulnerability can be described in order of decreasing sensitivity: neurons, oligodendrocytes, astrocytes, microglia, and cells of the capillary endothelium. Three types of anoxia are generally recognized: anoxic, ischemic, and cytotoxic.

The functioning of the nervous system in the presence of damage from toxic agents is obviously both of great importance and complexity. The nervous system possesses considerable redundancy of structure, which may mask functional change until the amount of damage exceeds the reserve capacity of the system.

The nervous system is also capable of developing tolerance or adapting to some types of damage; hence function may return to normal during continuous exposure to a toxic substance. Thus damage may exist in the nervous system that can be detected by cytologic or neurochemical methods when functional damage is not detected. On the other hand, alterations in gait, visual-motor performance, emotional state, and many other behavioral parameters may, at times, be the earliest and most sensitive signs of nervous system toxicity.

The neurotoxicants are classified, according to their primary toxic action, in the following types:

1. Anoxic damage to gray matter (neurons and astrocytes) with variation in pattern of damage depending on which of the three types of anoxia is produced;
2. Toxic substances causing lesions restricted to specialized CNS nuclear groups;
3. Damage to myelin from substances affecting oligodendrocytes of Schwann cells, resulting in encephalopathy if central white matter is involved or polyneuritis if peripheral cells are damaged;
4. Substances with a predilection for causing damage to axons of peripheral neurons;
5. Agents causing primary damage to perikarya of peripheral neurons;
6. Neurotoxicants causing damage to synaptic junctions of the neuromuscular system.

Psychoactive drugs induce primary toxic action to gray matter and specialized CNS nuclear groups, and can also potentially effect peripheral neurons and synaptic junctions, as a consequence of central damage.

The Autonomic nervous and Cardiovascular systems may also be affected because of specific effects of certain psychoactive drugs.

Drugs can selectively affect the heart or its vasculature. The effect can be solely functional, lasting only during the exposure period, and its magnitude is usually dose-related. The risk of irreversibility of the effect increases with the dose or duration of exposure. Generally, after a functional change in the heart, the risk of lethality is greater than that which occurs after changes in other parenchymatous organs. Sudden death due to arrhythmia contributes to a major portion of the mortality caused by a drug overdose. Chemicals can also produce structural, i.e., degenerative and inflammatory, changes in the heart or blood vessels, and these in turn lead to persistent functional changes. Cardiovascular functional effects develop after administration of a lethal dose of most chemicals and are usually secondary to the changes in other organ systems. Primary cardiovascular toxicity is the most common consequence of an exaggerated pharmacologic effect after an overdose of cardiovascular drugs. Similarly, other organotropic drugs, e.g., those affecting the central nervous system (CNS) or the autonomic nervous system, may also affect the cardiovascular system; their toxicity can be unrelated to the therapeutic action and thus is a side effect.

Nonmedical use of psychoactive drugs, e.g., amphetamines and hallucinogens can produce cardiovascular emergencies. These drugs increase the workload of the heart by increasing the heart rate and blood presssure and by provoking tachyarrhythmias. They may also indirectly lead to pulmonary edema, particularly in individuals with angina, hypertension, coronary atherosclerosis, or cerebrovascular disease.

Furthermore, anoxic or stagnant hypoxia results from exposure to psychoactive drugs that depress respiration. Anoxic hypoxia is characterized by a lower-than-normal PO_2 in arterial blood when oxygen capacity and rate of blood flow are normal or elevated. Stagnant hypoxia is characterized by a decreased rate of blood flow.

Disposal of the psychoactive drugs in large amounts may overload the organs involved in their metabolism and excretion, such as liver and kidney.

"*Liver* injury" is not a single entity, and the lesion observed depends not only on the chemical agent involved but also on the period of exposure. After acute exposure one usually finds lipid accumulation in the hepatocytes, cellular necrosis, or hepatobiliary dysfunction, whereas cirrhotic or neoplastic changes are usually considered to be the result of chronic exposure.

The hepatic lesions are divided into two categories on the basis of a classification for drug-induced liver injury. Type I lesions are those which are predictable, dose and time-dependent, occurring in most, if not all, subjects exposed to appropriate doses of the causative substances.

Type II lesions are those which are nonpredictable, and time-independent, occurring sporadically and often become apparent only after monitoring a large number of exposed individuals.

Five groups of morphological reactions are formulated:

1) zonal hepatocellular alteration without inflammatory reaction
2) intrahepatic cholestasis
3) hepatic necrosis with inflammatory reaction
4) unclassified group
5) hepatic cancer.

For most of the psychoactive drugs a direct toxicity and immunological combined mechanism has been postulated for the pathogenesis of adverse hepatic drug reactions (Figure 1).

Figure 1

DRUG

GENETIC AND ENVIRONMENTAL FACTORS

REACTIVE METABOLITES

BIND TO HEPATOCYTE
MACROMOLECULES

DENATURATION AND
ALTERED ANTIGENICITY

GENETIC FACTORS
DETERMINING
IMMUNE REACTIVITY

DIRECT HEPATOTOXICITY
(MILD, COMMON)
(SEVERE, UNCOMMON)

IMMUNE MEDIATED
HEPATOTOXICITY
(SEVERE, UNCOMMON)

Source: D.M. Davies, 1985

Because of the high renal blood flow, any drug in the systemic circulation will be delivered in relatively high amounts to the kidney. As salt and water are reabsorbed from the glomerular filtrate, the materials remaining (including the potential toxicant) in the urine may be concentrated in the tubule. Thus a nontoxic concentrate of a drug in the plasma could become toxic in the *kidney* subsequent to concentration within the urine.

The effects on kidney function may be brought about in one of several ways:

1) Vasocostriction could decrease renal blood flow and glomerular filtration rate, reducing urine flow, eventually resulting in an increase in BUN (blood urea nitrogen); if prolonged, vasoconstriction would lead to tissue ischemia with resultant loss of function and, eventually, tissue destruction;

2) Direct drug affection of glomerular elements, altering permeability such that filtration at the glomerulus is compromised;

3) Alternatively, or in combination with these other possibilities, the administration of a nephrotoxicant could influence function directly; either specific reabsorptive or secretory mechanisms could be influenced by the toxicant, or the general permeability of the tubule could be influenced such that the normal ability of the tubule to act as a barrier to diffusion could be altered.

Lack of self-care, malnutrition, uncleanliness, and probable involvement of the reticuloendothelial sytstem by some chemicals may affect the immunity of the addicts and may make them infection prone.

The interaction of drugs with lymphoid tissue may alter the delicate balance of the *immune system* and result in four types of undesirable effects: immunosuppression, uncontrolled proliferation (i.e., leukemia and lymphoma), alterations of host defense mechanisms against pathogens and neoplasia, and allergy or autoimmunity.

Furthermore, use of unsterile chemicals, syringes, and other paraphernalia for preparation of injectable drugs may lead to many infective processes such as viral hepatitis and bacterial endocarditis. Some characteristic marks may be left on the skin and other sites as a result of such parenteral drug administration (Pradhan and Dutta, 1977).

The toxic effects of drugs on the *human reproductive system* have become a major health concern: incidences of chemically induced germ cell damage and sterility appear to be on the increase. Experimental results suggest that a large number of chemicals including alcohol, amphetamines, narcotic and non-narcotic analgesics, monoamine oxidase inhibitors, marijuana and hallucinogens, solvents and other industrial chemicals affect male and female reproduction. However, an understanding of the underlying biologic mechanisms of reproductive toxicity remains incomplete and the predictiveness of laboratory animal studies for humans is still not generally accepted.

Changes in the outlook and attitude toward social and sexual life, and less restrained sexual contacts, may increase the incidence of venereal disease among addicts, many of whom are forced into prostitution to maintain their drug habits.

Drug Interactions

Problems in predicting drug effects arise when multiple drug usage occurs. Polydrug abuse, defined as a primary dependency on a psychoactive drug or drugs other than heroin, methadone or alcohol, may involve quite varied and complex mechanisms in producing drug interactions, which are often influenced by patient and drug administration factors. Polydrug abuse is generally categorized into three types: use of combinations of drugs in a single preparation; concomitant use of separate drugs; sequential or cyclic use of different substances. Polydrug abuse of the combination type may be self-imposed or result from additives, impurities, precursors, and substitutions that the users continue to abuse unknowingly along with the primary drugs of abuse. Concomitant abuse of drugs is generally practiced with the purpose of either potentiating or reducing the effects of one drug by the other. To regulate the time-course of action of an abused drug, users often resort to abuse of another drug having opposite pharmacological action. Limited scientific information exists on the behavioral and organ toxicity qualitative and quantitative consequences of most psychoactive drug combinations (Pradhan and Dutta, 1977).

Interactions of hallucinogens and some possible interactions of drugs of abuse at various neuronal sites are summarized in Tables 1 and 2. These receptor or nonreceptor mediated interactions produced a multitude of physiological, biochemical and pharmacological consequences that make impossible any classification of the potential adverse reactions. The magnitude of the quantitative pharmacokinetic and pharmacodynamic effects arising from the combination of drugs may, however, be restricted by the physiological system.

Effects and Mortality

The CNS and miscellaneous effects of short and long term use, and mortality related to various functional and organ systems, resulting from hallucinogens (except marijuana), amphetamines, fentanyl and meperidine analogues and methaqualone are dealt with in the following paragraphs.

Table 1

Interaction of Hallucinogens With Other Drugs

Hallucinogen	Interacting drug	Effect
LSD	Chlorpromazine	Partial antagonism to LSD; recognition of threshold dose elevated; enhanced orthostatic hypotension
	Phenoxybenzamine	Same as chlorpromazine
	Ergotamine	Intensification and prolongation of psychic symptoms
	Reserpine	Marked attenuation of subjective experience
	Isocarboxazide	Marked attenuation of subjective experience
	Progesterone	Very slight effect on psychomotor and intellectual impairment
Mescaline	Amphetamine	Potentiation of hallucinogenic effects
JB-329	Tetrahydroaminacrine (THA)	Antagonism
	Yohimbine	Antagonism

Source: S.N. Pradhan and S.N. Dutta, 1977, modified.

Table 2

Possible Interactions of Drugs of Abuse at Various Neuronal Sites*

Drugs of abuse	Sites of interaction	Effects produced	Possible interaction with
Morphine and related drugs	Cholinergic/adrenergic nerve terminals	Blockade of ACh release, of NE	Reserpine, AChE inhibitors, MAO inhibitors, amphetamines
LSD and other indolamines	Catecholamine storage vesicles	Release of NE, depletion of NE	Reserpine, MAO inhibitors, amphetamine
Mescaline	Catecholamine storage vesicles	Release of NE	Amphetamine, chlorpromazine
Amphetamine	Catecholamine storage vesicles (midbrain)	Release of NE and blockade of NE reuptake resulting in depletion	Tricyclic antidepressants, cocaine

*ACh, acetylcholine; NE, norepinephrine; AChE, acetylcholinesterase; MAO, monoamine oxidase.

Source: S.N. Pradhan and S.N. Dutta, 1977, modified.

Hallucinogens

Hallucinogens include a wide variety of structurally dissimilar substances, ranging from synthetic products to natural substances occurring in many plant species.

The terms hallucinogen, psychotomimetic and psychedelic are generally used to signify substances that produce changes in perception, thought and/or mood without serious disturbances in the autonomic nervous system and serious dependence.

According to structural similarity hallucinogens can be placed in classes, such as LSD, mescaline and MDA, PCP and ketamine, atropinic drugs, and pethidine derivatives.

The LSD class of indolealkylamines includes LSD (d-lysergic acid diethylamide), LSA (d-lysergic acid amide), psilocybin, DMT (dimethyltryptamine) and DPT (dipropyltryptamine).

The mescaline and MDA class, known as the phenylethylamine group, includes mescaline, MDA (3,4-methylenedioxyamphetamine), PMA (para-methoxyamphetamine), PMMA (para-methoxymethamphetamine), DOM or STP (2,5-dimethoxy-4-methylamphetamine), TMA (trimethoxyamphetamine), and MMDA (3-methoxy-4,5-MDA).

PCP (phencyclidine) and ketamine belong to the arylcycloalkylamine class of drugs which includes PCE (eticyclidine), PHP (rolicyclidine) and TCP (tenocyclidine).

The atropinic class includes atropine, scopolamine, and hyoscyamine which are also designated solanaceous alkaloids because they are derived from many species of the family.

The Pethidine derivative class includes JB-318 (N-ethyl-3-piperidyl benzilate), JB-329 (N-ethyl-3-piperidyl phenylcyclohexylpentylglycolate), JB-336 (N-methyl-3-piperidyl benzilate), MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), and PEPAP (1-phenethyl-4-phenyl-4-acetoxypiperidine).

Virtually all of the hallucinogens can produce acute adverse effects, spontaneous and drug-free recurrence of flashbacks (feelings, perceptions originally experienced during a hallucinogenic episode), and amotivational syndrome.

Rapidly developing tolerance, as tachyphylaxis or cross-tachyphylaxis, is known to occur to the effects of the LSD, mescaline, phencyclidine, and atropinic classes to a limited extent in humans.

Physical dependence on any of the hallucinogens is not known to occur, although psychological dependence on LSD and phencyclidine has been reported in chronic heavy users.

CNS Effects

Effects of hallucinogens vary considerably depending on the drug, its type, and dose; the set of the subject (whether the user is a psychiatric patient or a volunteer, nature of the individual) and expectations of the subject or the experimenter; and the setting of the clinical experiment. Of these, variations in the subject's drug use experience appear to be very important and may occur in several ways.

The hallucinogenic effects of short term use (Jaffe, 1980) in humans mainly consist of striking psychological effects and relatively few physiological effects. The latter include some sympathomimetic effects (mydriasis, tachycardia), stimulated respiration, hyperreflexia, and occasional ataxia at high doses. Changes in blood pressure, pulse rate, and respiration, elevation of body temperature and sweating, nausea and vomiting, which may be quite variable, reflect varying levels of induced anxiety rather than primary pharmacological effects.

The psychological effects are numerous and diverse, and depend not only upon the dose but also upon the set and the setting. Hallucinogens can also induce a hypersuggestible state and under its effect, the rational, critical function of the mind is set aside and the expectations of the subject and the experimenter influence responses enormously.

Early effects can include numbness, muscle weakness, muscle twitching, rapid reflexes, tremulousness, impairment of motor skills and coordination, and pupillary dilation. Often there is early anxiety or sometimes exhilaration; the latter is likely due to the user's expectations, as it may occur prior to the onset of hallucinogenic actions. Seizures have also occurred, although rarely.

Later effects can include the following: perceptual distortions, usually visual; body image, space and time distortions (minutes may seem to pass as slowly as hours); diminished control over thinking processes and concentration; synesthesias (one sensory modality is melded with another); recent or long-forgotten memories blend with current experience;

over-attention to parts of the user's body or on trivial objects; perception of brighter colors, sharper definition of objects, increased hearing acuity, etc.; simultaneous existence of different emotions; withdrawal from and indifference to their surroundings; hypervigilance; and many alternations between these states; feeling of mystical, religious, or "cosmic" experience.

Long-term effects of hallucinogen use can include flashbacks, amotivational syndrome, and psychosis (Cox *et al.*, 1987). The phenomenon frequently associated with hallucinogen use is "flashbacks"—spontaneous recurrences of specific experiences which originally occurred during hallucinations. Typically they are brief, lasting only a few minutes. They may occur shortly after an LSD episode or, in some cases, up to four or five years later. Flashbacks may be perceptual, somatic and emotional. Visual images are by far the most frequently reported form of flashback, ranging from formless colors to very frightening hallucinations. Pseudohallucinations involving geometric patterns are the most common sort of flashback. Less frequently, flashbacks involve other sensory modalities—taste, smell, hearing, body sensations, touch, and balance. They may also recur in the form of distortions of time, space, body image, or reality. Their etiology is unknown.

An amotivational syndrome has been observed in some users of hallucinogens. The common manifestations of this syndrome are increasing apathy and decreasing interest in both one's environment and social contacts, loss of effectiveness, passivity, diminished frustration tolerance, and lack of interest in planning ahead. In some respects the use of LSD and other drugs may serve to foster the amotivational syndrome in some users, and amotivational syndrome as a lifestyle may serve to foster the use of LSD and other drugs in others.

Acute psychotic episodes caused by a single dose of hallucinogens ordinarily last for several hours. However, both a single dose and chronic use have resulted in a protracted period of psychosis for some individuals; this psychosis in many respects resembles paranoid schizophrenia and is characterized by true hallucinations (mainly visual), delusional thinking, and bizarre behavior. Although many of these individuals are believed to have been latent psychotics prior to their use of LSD, a few had previously exhibited little or no obvious personality disturbance. The issue is yet to be fully resolved as to whether or not chronic psychosis precipitated by LSD is a diagnostic entity distinct from schizophrenia, although the weight of evidence suggests that such a distinction is probably not warranted. Indeed, there are many more similarities between these two groups than differences.

Many users have experienced adverse reactions to the effects of LSD (Jaffe, 1980; Strassman, 1984). Fearfulness, anxiety, and depression may occur even in experienced users who have had no prior adverse reactions. Acute paranoid states may occur, and bizarre delusions may be manifested in such extremes as violent, homicidal, or suicidal behavior. Severe confusion and disorientation may also provoke highly inappropriate behavior. Nonetheless, in spite of their severity, these symptoms usually decline rapidly in intensity and disappear after the drug is metabolized and excreted from the body.

CNS effects of the hallucinogens are very similar in many respects despite differences in their chemical structure. Comparative studies using different doses of the drugs have shown qualitative similarities although slight differences were noted in the intensity of some effects.

Mescaline, DET and DMT are shown to have a slower onset and longer duration of effects than LSD. Mescaline produces a greater increase in deep tendon reflexes and more anxiety, depersonalization, and disorder of space perception than LSD and psilocybin which, however, evoke more euphoria. Psilocybin produces a shorter duration of action, a more agreeable response and introspection without marked impairment of faculties.

Phencyclidine is the only drug which produces impairment in the functions measured (such as attention, motor skills, proprioception) and also in tests of symbolic and sequential thinking, whereas LSD and psilocybin produce effects on sensory perceptions (Fauman and Fauman, 1978; Lerner and Burns, 1978). The effects of the piperidyl benzilate esters (JB-318 and 329) and other pethidine derivatives (MPPP, MPTP, PEPAP) are different from those of LSD, mescaline, psilocybin, DMT, and other hallucinogens. The effects of large doses persist up to 12 hours and produce a syndrome resembling a toxic delirium produced by scopolamine and other belladonna alkaloids (at high doses), and predominantly characterized by mental confusion, disorientation, memory loss, and marked impairment of speech.

Perceptions of the external environment produced by harmaline and harmine are usually not as greatly affected as with other hallucinogens, and delusions and feelings of unreality generally do not occur. Furthermore they do not exert significant effects on thought processes.

High doses (300 mg) of TMA produce at least one effect which usually does not occur with higher doses of mescaline and related compounds: a tendency toward unprovoked antisocial behavior, manifested as anger or hostility toward others and, sometimes, grandiose beliefs about oneself. Abusers of central nervous system stimulants are usually hyperexcitable, hyperactive, agitated, and may be in a state of acute psychosis. Although theoretically it would seem easy to recognize and separate these groups of patients, in practice this should not be relied upon heavily for diagnosis and therapy. In severe poisoning these patients may become comatose with an initial phase of stimulation, high fever, and convulsions. Coma may also be the result of the effects of central nervous system depressants (e.g., diazepam or a similar drug) used to counteract the effects of the stimulants or result from associated illness or injury.

Miscellaneous Effects

In addition to CNS effects, genetic abnormalities, brain damage, retinopathy and other miscellaneous effects have been reported (Aptekar, 1970). In spite of the chemical structural differences a number of hallucinogens produce similar adverse effects. Due to adrenergic and anticholinergic properties, both Mescaline-MDA and Atropinic classes, induce, for instance, pupil dilation, increased pulse and breathing rate, urinary retention, etc.

There is inconclusive evidence in humans of chromosomal damage resulting from chronic hallucinogen use, and the significance of such damage is also unclear. LSD and mescaline cross the placenta and induce fetal neural and other malformations in experimental situations. There appears to be a higher risk of spontaneous abortion and congenital abnormalities in offspring of women who have regularly used LSD during pregnancy; however, in almost all instances studied, the mothers had also used other drugs during their pregnancy, and therefore casual relationships are difficult to determine (Dumars, 1971).

Although there has also been concern about the possibility of brain damage in chronic users, again causality has not been established. On the whole, studies have found no consistent differences between hallucinogen users and non-users on tests designed to elicit brain impairment.

LSD causes neuronal changes in rats, both in vivo and in vitro, but only with massive doses. Because of the rapid build-up of tolerance and lack of physiological dependence, chronic compulsive abuse of LSD is not common. Adverse neurological effects are infrequent but some of these may well go undetected and unreported since these drugs are usually taken without medical supervision. Grand mal seizures, although rare, have been reported as occurring about an hour after ingestion of LSD. It is possible that arteriospasm may be involved in the production of some LSD-related mental disorders. In the dosages usually employed LSD has an activating effect on the human EEG with a decrease in the amount of slower activity. Objective and subjective neurological deficits were accentuated and changes occurred in the EEG pattern in subjects who were given LSD. Generally, there was decreased asymmetry with a decrease in amount or amplitude or both of slow wave activity and a more normal appearing EEG. Grand mal seizures developing to a focal neurological deficit four days later, also occurred in a case of carotid artery obstruction after ingestion of an unknown quantity of LSD capsules (Logan, 1975). This complication has been likened to those seen with methysergide which has been known to produce vascular complications.

Alterations in visual and somatosensory evoked potentials and an increase in the B-wave of the retinogram are also seen. LSD users tend to be attracted to bright and colorful objects because of their heightened degree of awareness of visual imagery, and they may gaze at the sun. Since the drug also causes mydriasis, such sun-gazing would result in a higher concentration of light energy being delivered to the macula and produce solar retinopathy characterized by decreased visual acuity, central scotoma, and/or chromatopsia. Two cases of such solar retinopathy have been reported in young patients who gazed at the sun while under the influence of LSD (Schatz and Mendelblatt, 1973).

The major cardiovascular side effect of most of the hallucinogens is their effect on blood pressure (Blanck *et al.*, 1973; Felmer *et al.*, 1974). Administration of LSD in moderate dosage in anesthetized dogs produces depression of left ventricular function and contractility with moderate bradycardia. Tachyarrhythmias are more frequently observed in subjects abusing hallucinogens and probably account for most of the sudden deaths noted after large amounts are consumed. DOM (STP) may produce potentially lethal arrhythmias.

Cases of gangrene of the extremities unclearly resulted, after LSD ingestion, from focal infection or from vascular LSD effects. Serious necrotizing angiitis, clinically and histopathologically indistinguishable from periarterite nodosa with renal, gastrointestinal and cardiac involvement have been described in association with the intravenous use of narcotics, stimulants and hallucinogens (Citron *et al.*, 1970; Halper and Citron, 1971).

Myoglobinuria and acute renal failure have followed violent isometric muscle contractions after self-administration of phencyclidine or lysergide (Foster, 1974; Blain and Lane, 1983; Blain, 1984).

Hallucinogen use has also been alleged to cause vasoconstriction capable of producing ischemia so severe that even minor infection may result in massive tissue necrosis and terminal amputation.

In heavy cigarette smokers the severity of ischemia is further increased because of peripheral vasoconstriction caused by absorbed nicotine. Retroperitoneal fibrosis in adults has been finally reported as a possible effect of LSD (Aptekar, 1970).

However, establishment of a causal relationship between the hallucinogens and these complications should be made cautiously.

Mortality

Every hallucinogen can cause overdose characterized by coma, high fever, convulsions and/or paralysis, cardiovascular collapse, respiratory arrest and death (Pradhan and Dutta, 1977; Cox *et al.*, 1987).

No deaths in humans resulting from acute LSD or psilocybin dose have been reported. However, cases of suicide during or following LSD intoxication have occasionally occurred. Other results of violent or hazardous behavior have included accidental (sometimes bizarre) fatalities and very infrequently homicides and self-mutilations.

Because harmaline and harmine are monoamine oxidase inhibitors, they can produce severe and potentially lethal effects of the heart and blood pressure when taken concurrently with any of a wide range of common foods containing tyramine (e.g., aged cheeses, chocolate, red wine) or with CNS-depressant drugs.

A relatively small number of MDA/PMA-associated deaths resulting from respiratory insufficiency have been reported. It is likely that there are others that have remained undocumented, although reports of MDA-associated deaths continue to appear in the clinical literature from time to time. It is important to note that more dangerous drugs such as PMA (paramethoxyamphetamine) and PCP (phencyclidine) have been sold on the street as MDA (Cox *et al.*, 1987).

Deaths from acute overdose of PCP have occurred with amounts estimated to be between 150 and 200 milligrams. While the usual clinical picture is coma, convulsions, and respiratory arrest, the following have also been reported to result from extremely high doses of PCP: repeated uninterrupted convulsions, acute hypertensive crisis, hemorrhage of the blood vessels of the brain, and kidney failure. Overdose may also be complicated by the simultaneous presence of other drugs in the body. High doses of CNS-depressant drugs (e.g., sedative/hypnotics or narcotics) substantially increase the risk of respiratory arrest (Fauman and Fauman, 1978). Children are particularly sensitive to the effects of atropinic drugs, and doses as small as 10 milligrams are sometimes fatal to them. Nowadays, however, fatalities among adults are rare and usually result from severe overdose.

Although much less frequently than with other amanitas, deaths occasionally result from ingestion of *Amanita muscaria* which may contain atropine-like alkaloids and bufotenine. A lethal overdose causes delirium, convulsions, deep coma, and death from cardiac arrest.

Amphetamines

The class of drugs known as stimulants contains widely disparate groups of substances, including amphetamine and methamphetamine, which increase activity of the central and autonomic nervous system.

Abuse of amphetamine and methamphetamine has declined during the past decade due to severe restrictions of medical use and more intense police action against illicit production and trafficking.

Long abused for euphoric and stimulant effects, these drugs can create, at high dose levels, a toxic psychosis characterized by paranoid delusions, hallucinations, and, frequently, aggressive or violent behavior.

CNS Effects

Effects of amphetamines vary depending on the dose and route of administration, nasal, oral or intravenous, the latter being the preferred method of the chronic high-dose abuser.

In low to moderate doses, most drugs which stimulate the CNS can cause heightened feelings of well-being, and at high enough blood levels many such drugs produce intense euphoria. Stimulants may also increase wakefulness and mask the signs of fatigue, prolonging the user's ability to perform work requiring endurance or normal levels of concentration.

Stimulants can also produce insomnia and can interfere with normal sleep. As well, stimulants tend to suppress appetite and reduce hunger pangs (Pradhan and Dutta, 1977; Cox *et al.*, 1987).

Chronic abuse of very high doses of amphetamines (especially methamphetamine by injection) can result in serious psychological consequences, ranging from chronic agitation and anxiety states to toxic psychosis. When injected intravenously, methamphetamine produces powerful sensations referred to as a "rush."

One of the more frequently observed phenomena among those who chronically use amphetamines, and amphetamine-like drugs is a state of overstimulation, agitation, insomnia, and anorexia. Users often resort to cannabis, narcotic analgesics, or sedative/hypnotics in order to combat these adverse effects, as well as for these drugs' own euphorigenic properties. In fact, CNS-depressant drugs (including alcohol) are so frequently and widely consumed by amphetamine-dependent users that multidrug dependence is quite common. On the other hand, many heroin addicts seek amphetamines and/or cocaine for their euphoric properties, particularly when they are no longer able to achieve appreciable euphoric effects from their regular dose of heroin.

The effects of short-term use at low doses include: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, mild confusion, tremor, and, in rare instances, panic and/or psychotic episodes; reduction of appetite; increased alertness and energy, reduction of fatigue and drowsiness, a general increase in psychomotor activity and a heightened sense of well-being; an increase in libido, possible temporary impotence and increased urine output (Cox *et al.*, 1987).

At higher doses, intensification of the low-dose effects may occur as well as any of the following effects: intense exhilaration and euphoria, rapid flow of ideas, feelings of increased physical strength and mental capacity, garrulousness, excitation, agitation, and sometimes panic or in some cases depression and irritability; paranoid thinking, confusion, and perceptual distortions including hallucinations; assaultive behavior.

The effects of long-term use at low doses or higher doses can include: chronic sleeping problems including insomnia, frequent nocturnal awakening, and poor-quality sleep; anxiety and tension stress; appetite suppression, which may result in disorders related to nutritional deficiency.

Regular high-dose use can also directly produce suspiciousness and paranoid thinking, severe agitation, and in some cases chronic amphetamine psychosis (Cox *et al.*, 1987).

Amphetamines are reputed to produce chorea which usually presents as irregular, jerking, involuntary movements of the limbs. Often the slow writhing movements of athetosis or a dystonia are superimposed. The patient frequently attempts to disguise the movement by converting it into some reasonable action (Blanck *et al.*, 1973).

In addition to true hallucinations, psychotic symptoms, including paranoid delusions, often emerge and may intensify during the course of a "run" or chronic use of injectable methamphetamine. Uncontrolled and violent behavior may therefore occur. Frequently, seemingly meaningless and bizarre behavior may also be compulsively repeated. In many respects, this toxic state, referred to as amphetamine psychosis, closely resembles paranoid schizophrenia. However, the two states differ in that during amphetamine psychosis the consciousness remains clear and accurate orientation in regard to time, place, and self identity is maintained.

Tolerance to many of the significant effects of the amphetamines has been reported to develop when these drugs are chronically administered. Cross-tolerance between amphetamines and other amphetamine-like CNS-stimulants has been clinically observed.

It is still questionable whether chronic high-dose use of amphetamines results in physical dependence and a characteristic withdrawal sickness. When chronic use is abruptly discontinued, the clinical picture of withdrawal does not include major grossly observable physiological disruptions. Rather, the prominent symptoms are extreme fatigue followed by prolonged but disturbed sleep. Upon awakening, the appetite is quite voracious. Irritability, lassitude, and moderate to very severe emotional depression also typically occur. Occasionally, sleep disturbances and psychotic symptoms persist after the period of prolonged sleep; this syndrome usually clears after several days of abstinence, although depression and irritability may continue to occur for a more extended period of time. Therefore, rather than certainly physical, an emotional dependence may occur.

Marked psychological dependence frequently results even among regular low-dose users. In this case, psychological dependence is characterized by a preoccupation with and compulsive need to continue taking the drug because of those psychological effects which the user deems to be favorable. Certain of the drug effects are craved so intensely that, if the drug is temporarily unavailable, severe distress or even feelings of panic are experienced.

Miscellaneous Effects

Among the more significant autonomic nervous system effects which many stimulants exert on the body, and which are generally regarded as unfavorable side effects, are dilation of the pupils, increased heart rate and blood pressure, constriction of the blood vessels, increased rate of respiration, dryness of the mouth, unpleasant taste, diarrhea; retraction of the gum tissues, and skin rush, symptoms collectively described as the alarm reaction. At higher doses anginal pain, fainting, cardiovascular collapse, excessive sweating, and fever may occur.

Sympathomimetic anorexiants have been used widely in early pregnancy, and amphetamines have been suspected of teratogenic effects. An increase in cardiovascular anomalies, biliary atresia and congenital abnormalities have been reported in children whose mothers had taken amphetamines in early pregnancy (Levin, 1971).

Spontaneous subarachnoid hemorrhages and intracerebral hematomas have been described in association with oral and intravenous use of amphetamines (Goodman and Becker, 1971). These are probably related to the hypertensive effect of the drug and a possible preexistent, vascular lesion, such as an intracranial aneurysm or an arteriovenous malformation. The clinical manifestations are acute and include lethargy, coma, evidence of meningeal irritation, and a focal neurological deficit. Motor, sensory, or visual field defects can occur in addition to symptoms of acute intoxication in a chronic abuser. Reversible dyskinesias have been reported (Logan, 1975). Chronic vascular changes, loss of neurons, and proliferation of glia have been observed in rabbits, however, it is not clear whether these drugs produce a direct neurotoxic effect.

Acute hallucinogenic drug crises with amphetamines are frequently associated with hypertension and tachycardia. Amphetamines, when administered parenterally or even orally, can cause severe hypertension, occasionally complicated by either the above-mentioned cerebrovascular accidents or cardiovascular collapse (Goodman and Becker, 1970). Electrocardiographic abnormalities consisting of bradyarrythmias, conduction disturbances, and depolarization and repolarization abnormalities are common in drug addicts. Paroxysmal atrial fibrillation is not uncommon in heroin users who also abuse amphetamine (Lipski *et al.,* 1973). Tachyarrhythmias and pulmonary hypertension are more frequently observed in persons abusing amphetamines and probably account for most of the sudden deaths noted after large amounts are consumed.

Arterial complications result from drug injection into a peripheral artery. With progressive obliteration of venous injection sites, an addict may occasionally turn to intra-arterial injection either because the artery remains a palpably localizable access to the circulation or because the addicts desire the special sensations known as a "flash" or "handtrip" that results from intra-arterial injection. A "hit" in the brachial or radial artery causes a burning paresthesia throughout the arterial distribution and a hyperemic flush followed by a spasm of the artery with consequent ischemic symptoms. The vascular lesion in a "hand trip" has several causes. Intimal damage secondary to the drug with necrosis of the arterial wall has been thought to give rise to thrombus propagation in the arterial tree. Extreme vasoconstriction has also been postulated secondary to catecholamine release from the injured artery. Volkmann's ischemic contracture results from intra-arterial injection of amphetamines (Lindel *et al.,* 1972). Microaneurysms of the kidney and liver have been described in patients who take amphetamines intravenously.

Direct intra-arterial injection may result in embolization of particulate matter to peripheral blood vessels. This, in association with superimposed thrombosis, infection, or foreign body reaction, may cause vascular obstruction in the arterial system at a site distant from injection; particulate embolization has a predominant role in the production of tissue ischemia.

Most of the pulmonary emboli associated with drug abuse are septic and have their origin from either an infected subcutaneous, intramuscular, or intravenous injection site or infective endocarditis of either the tricuspid or pulmonic valve. The embolic material from the injection site and that from right heart endocarditis is usually bacterial. Septic pulmonary emboli are common enough in drug addicts to give rise to the radiographic picture called "mainliner's lung" consisting of multiple, bilateral, pulmonary lesions.

Vascular changes resembling necrotizing angiitis have been demonstrated pathologically and radiographically in patients abusing various drugs or drug combinations that often contain methamphetamine (Citron *et al.*, 1970). A serious necrotizing angiitis having the clinical and histopathological characteristics of periarteritis nodosa with severe renal, gastrointestinal, and cardiac involvement has been described in association with the intravenous use of methamphetamine (Citron *et al.*, 1970). The clinical manifestations depend on the intensity of the reaction, the distribution and location of the lesions as well as the duration of the disease. The persistence of the etiological agent in the body appears to bear on the progress of the disease. Pancreatitis, synovitis, renal failure, hypertension, recurrent pulmonary edema, peripheral neuropathy, arthralgias, and myalgias have been common. The patients have also shown a deterioration of visual acuity, apparently because of retinal angiitis. Methamphetamine alone or in combination with heroin is commonly used by these patients.

Stimulation of ACTH production occurs following administration of amphetamines and this may interfere with measured ACTH values (Besser *et al.*, 1969). Drugs may damage muscular tissue in several ways. Rapidly progressive multiple mononeuropathy, possibly on an allergic basis, has been reported. Biopsied specimens of the sural nerve and gastrocnemius muscle disclosed a necrotizing angiitis involving the medium and small sized muscular arteries, arterioles, veins, and venules. Destruction of the elastica with microaneurysm formation and thrombi was superimposed on regions of necrosis. The changes were typical of hypersensitivity-type angiopathy and seemed related to methamphetamine, since this was the only drug in use. However, adulterants could have played a role as pathogenic factors.

Muscle damage, functional or anatomical, or both, may occur as a rare adverse effect of amphetamine abuse. It is a feature of drug-induced myasthenia and myopathy. The injury may be primary, due to a direct action of the drug on muscle tissue, muscle metabolic enzymes, or neuromuscular transmitters; or secondary, when it follows hypokalaemia induced by the drug concerned (Kendrick *et al.*, 1977). It is also a feature of polymyositis, and dermatomyositis disorders occasionally precipitated by drug allergy. When muscle necrosis is minimal, it may manifest itself only by myalgia or a rise in the concentration of serum enzymes originating in muscle, or both, but when it is very severe myoglobinuria may occur. Some mild cases of drug-induced myalgia which have either shown no electromyographic or biochemical abnormality or have not yet been studied in this way may possibly have underlying functional or anatomical lesions, or both.

A more severe form of necrotizing myopathy, known as rhabdomyolysis and usually accompanied by myoglobinuria, may be caused by any of the drugs that produce an acute or subacute painful myopathy (Kendrick *et al.*, 1977). However, the disorder is most often seen with drugs of abuse such as opiates, amphetamines, phencyclidine and alcohol.

The onset is acute with severe muscle pain, tenderness, and swelling. Generalized weakness is often found, the proximal muscles being more severely affected than the distal, and patients may be areflexic. Seizures and coma or depression of the level of consciousness may occur and about half the cases develop acute renal failure secondary to acute tubular necrosis. Serum muscle enzymes and myoglobin levels are grossly elevated and electromyography in the acute phase shows myopathic changes frequently associated with increased spontaneous insertional activity due to surface membrane damage. Biopsy at this stage may show severe necrosis, with nearly every muscle fiber in the section destroyed. However, in milder cases the changes may be slight with scattered focal necrosis, phagocytosis, and degeneration. Inflammatory infiltrates may also be seen.

Injected amphetamines may affect the liver directly and also alter immunoglobulin production (Davis *et al.*, 1970).

A generally poor state of health and lowered resistance to disease is common among heavy users. Their condition is usually due to such indirect effects as poor nutrition, postponement of adequate medical treatment, and insufficient sleep.

Frequent injection of methamphetamine can result in communicable and potentially serious diseases such as viral hepatitis, septicemia, acquired immune deficiency syndrome (AIDS), and bacterial endocarditis. The latter is one of the most common and serious septic complications of parenteral drug abuse. In contrast to the commonly taught presentation of endocarditis as a subacute disease, the heroin or amphetamine user usually presents with the syndrome of acute endocarditis (Tuazon, *et al.*, 1975). The tricuspid valve is almost always involved, murmurs are frequently absent, and such patients present simply as staphylococcal septicemia. Pulmonary findings in the form of infiltrates or typical septic emboli, in the absence of peripheral venous disease, are common.

Various other secondary septic complications can result from septicemia with the staphylococci. For example, meningitis, septic arthritis, osteomyelitis, and metastatic abscesses to the brain, kidneys, spleen, and liver as well as mycotic aneurysms are often encountered. Involved heart valves are rapidly destroyed and congestive heart failure may progress quickly. Arrhythmias are common and infarction secondary to coronary emboli as well as myocardial abscesses may cause sudden death. It is widely recognized that drugs can produce nasal obstruction, nasal bleeding, and anosmia.

Amphetamines lose vasoconstrictor activity if used over a long period, and produce an increasing amount of after-congestion. The chronic and often severe mucosal swelling thus produced can cause extreme narrowing of the nasal passages. Many patients obtain relief from their obstruction within a short time after stopping the drugs (Wilson and Schild, 1968).

A high incidence of caries has been observed in amphetamine abusers and this is due to both the reduced salivary flow rate and a decrease in salivary calcium and phosphate concentrations (DiGugno *et al.*, 1981).

Mortality

Deaths reported in the literature from acute overdose of amphetamines were directly caused by acute cardiac failure, hyperthermia and rupture or collapse of blood vessels in the brain. More frequent deaths have been caused by complications of intravenous administration (bacterial and viral infections, angiitis, etc.) and by pathologic conditions unrelated to specific actions of amphetamines but probably attributable to disease indirectly resulting from lifestyle. Numerous violent case reports of accidents, homicides and suicides have been attributed to amphetamine psychosis. Homicide victims often range from relatives and co-users to complete strangers. Heavy intoxication and a withdrawal syndrome are responsible for successful and attempted suicides. The number of unknown amphetamine-linked deaths from various causes may be, however, fairly high.

Meperidine and Fentanyl Analogues

Drugs classified as narcotic analgesics may be naturally-occurring, semi-synthetic, or wholly synthetic like meperidine (pethidine), fentanyl and their analogues. The primary pharmacological action for which narcotic drugs are administered is their ability to reduce sensitivity and emotional response to pain. At the weaker end of the scale are such drugs as meperidine analogues, 10 to 12.5 percent the potency of morphine as an analgesic. Their duration of action is from two to four hours and is retained when administered orally. At the other end of the scale are such drugs as fentanyl and its analogues. Fentanyl is 80 to 100 times more potent than morphine as an analgesic with a duration of action shorter than morphine and meperidine. Tolerance and both physical and psychological dependence can develop with long term meperidine and fentanyl use. Both meperidine and fentanyl are commonly reported drugs of abuse among physicians and nurses. A few deaths among anesthesiologists have been attributed to overdose of fentanyl, primarily used as premedication in anesthesia, and as an analgesic following surgery.

Over the past few years potent congeners of meperidine (MPPP and PEPAP) and fentanyl (alpha-methylfentanyl, para-fluorofentanyl and others) have been designed to circumvent drug laws and have surfaced on the streets of North America.

CNS Effects

The effects of short-term use of low doses of meperidine include: suppression of the sensation of and emotional response to pain; euphoria; mild clouding of mental function, drowsiness, lightheadedness, dizziness; mild depression and anxiety; visual disturbances; occasionally headache; reduced libido (Cox *et al.*, 1987).

Intensified effects may occur as the dose increases and include: sensitivity-decrease to painful stimuli; greater probability of sleep; ability-impairment to concentrate; pupillary dilation; occasionally CNS excitation manifested by muscle twitches and tremors.

The effects of short-term use of fentanyl are similar to those of other narcotic analgesics, although muscle rigidity and respiratory depression occur when the drug is rapidly injected via the intravenous route.

The effects of long-term use of meperidine are similar to those produced by most other narcotic analgesics (Cox *et al.*, 1987). At high prolonged daily doses (1–3 grams), agitation, toxic psychosis including hallucinations, seizures, persistent muscular twitches, tremors, hyperactive reflexes, and round skin scars on the arms have been observed. Within three hours after the last dose, mild withdrawal symptoms begin to appear.

When large doses are administered at short intervals the EEG shows changes characterized by low-frequency, high-amplitude waves, and abnormal slow wave activity persists even after development of tolerance. EEG evidence of convulsive activity has been reported in animals with larger doses of meperidine.

The hallucinogenic CNS effects of the meperidine analogues (MPPP, MPTP, PEPAP, JB compounds) are reported in the paragraph concerning the hallucinogens.

Miscellaneous Effects

The complications induced by meperidine and fentanyl are similar to those produced by most other narcotic analgesics. Like morphine these drugs depress respiration (rate, minute volume), stimulate the chemoreceptor trigger zone (CTZ) of the medulla, producing nausea, dry mouth and vomiting, and constrict smooth muscles of the ureter and biliary tract. The respiratory depressant effect is antagonized by narcotic antagonists (e.g., nalorphine, naloxone).

Cardiovascular effects of meperidine and fentanyl are essentially similar to those of morphine (Jaffe and Martin, 1975).

Fentanyl abusers have been known to take high doses with consequent effects similar to those of other narcotic analgesics and more significant respiratory depression is the principal danger following overdose.

Muscle damage, functional and anatomical, such as severe fibrosis and contracture, may also accompany repeated intramuscular injections (Foster, 1974; Blain and Lane, 1983; Blain, 1984). Severe and irreversible symptons clinically identical to those of Parkinson's disease may occur after several days of consecutive injection or snorting of MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a contaminant of MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), the latter also called "synthetic" heroin (Cox *et al.*, 1987).

MPPP, MPTP, PEPAP and JB meperidine derivatives are synthetic substances which closely resemble meperidine in chemical structure with more powerful effects. Although animal studies suggest that MPTP is devoid of opiate properties, it can produce, by injection or passive vapor inhalation and adsorption through the skin, highly damaging effects such as: slowed voluntary motor functioning to almost total immobility, difficulty in vocalizing, increase in muscle tone, rigidity, flexed posture, tremor, drooling and flattened facial expression. Quite high doses of antiparkinsonism drugs are required for symptom control and the disease may reveal itself years after exposure to MPTP (Langston and Ballard, 1983).

Mortality

At very high doses (i.e., overdose) meperidine can produce disorientation, hallucinations, grand mal seizures, deep sleep possibly progressing to stupor or coma, shallow and markedly slowed breathing, slow heart rate, low blood pressure, cyanosis, low body temperature, flaccidity of skeletal muscles and cold and clammy skin. Death from respiratory depression and cardiac arrest is induced by both meperidine and fentanyl and their congeners. The risk of fatal overdose appears to be greatest among users not tolerant to the toxic effects of meperidine congeners and of alphamethylfentanyl (AMF), para-flurofentanyl (PFF) and other fentanyl analogues, which do appear to be adequate substitutes for heroin.

Methaqualone

Methaqualone, originally introduced in 1951 as an antimalarial drug, and mecloqualone are quinazoline derivatives which possess sedative-hypnotic activity similar to that of short-acting barbiturates and chlordiazepoxide, and cause a sensual and somewhat euphoric state.

Prolonged use of methaqualone leads to development of tolerance and crosstolerance to other drugs with similar psychoactive effects and psychological and physical dependence. Abrupt cessation of methaqualone use in persons with a history of daily ingestion of 1.5 to 2 grams for several months causes withdrawal symptons characterized by restlessness, mental confusion, visual hallucinations, brisk reflexes, tremor, hyperthermia, generalized convulsions and delirium. Because of the potential for fatal convulsions occurring during sudden withdrawal, this drug is more dangerous than other sedative-hypnotics capable of producing physical dependence.

CNS Effects

The effects of the short-term use of methaqualone at low doses include: feelings of calmness and relaxation; drowsiness; dizziness, fatigue, or lethargy; restlessness, anxiety and prickling, tingling, or burning sensations or numbness of the extremities and headache (Cox *et al.*, 1987).

At higher dose levels the following effects may occur: mellow, sensual, and dissociative "high" effect, reportedly similar to that produced by heroin; drowsiness and sleep; general numbness or tingling sensation throughout the body, motor incoordination, slurred speech, muscle weakness, weakness of the knees and ankles, tremors, muscle spasms, restlessness and disorientation which may result in severe agitation or panic. Some users continue to experience several of these effects for up to 24 hours or, in a few instances, longer.

At higher doses, the respiratory depression produced by methaqualone is usually not as great as that produced by the barbiturates and most other sedative/hypnotics. However, when methaqualone is taken in combination with any of these drugs, life-threatening effects are intensified. Tremor of the hands and legs as well as muscular rigidity of the limbs has been observed in some cases of overdose.

It has been reported that the effects of long-term use of methaqualone are probably similar to those produced by long-term abuse of barbiturates and include impairment of cognitive and motor functions, visual disturbances, emotional instability, sleep dysfuntions including frequent insomnia, and fatigue (Cox *et al.,* 1987).

High dose abuse of the combination of methaqualone and diphenhydramine (Mandrax) has induced an acute toxic psychotic state characterized by delusions, hallucinations, disorientation and confusion which disappears within two to three days.

Methaqualone can alter the "man-machine interaction" that applies not only to the action and skills involved in driving a car, but to the operation of complex machinery. Laboratory studies and equally sound epidemiological investigations performed on sedative-hypnotics show that methaqualone use may more than double the risk of traffic accidents, and a number of fatalities have been attributed to the combined intake of methaqualone and small amounts of alcohol.

Miscellaneous Effects

Further side effects of low and high doses of methaqualone include: abnormally rapid heart rate; mild to moderate respiratory depression; dry mouth, loss of appetite, nausea and vomiting, stomach discomfort, and diarrhea; sweating and hangover; and profuse sweating, and chills.

A sensorimotor neuropathy may occur in long-term abusers of methaqualone. Sensory or sensorimotor distal polyneuropathies are probably the most commonly encountered drug-induced neuropathy.

Abusers display the classical symptoms and signs of a mixed peripheral neuropathy. They complain of a symmetrical distal sensory loss, often more severe in the lower limbs and characterized by glove and stocking distribution. There may be painful dysaesthesial and depressed tendon reflexes.

Xanthopsia, red and green vision have been described in patients on methaqualone (Davidson, 1973). Diplopia is a commonly noted adverse effect of methaqualone abuse but it is difficult to determine whether it was caused by an extra-ocular muscle palsy or by the breakdown of a phoria. Probably in most instances the drug caused a breakdown of a phoria through its effect on central fixation reflexes (Davidson, 1973). Bullous eruptions have been observed in abusers of methaqualone and diphenhydramine (Pinkus, 1971).

Mortality

In addition to serious injuries and traffic fatalities often reported deaths have been attributed to the combined intake of methaqualone and alcohol and other depressant agents. In severe poisonings (manifested by coma, hypertonicity, hyperreflexia, myoclonia and grand mal seizures) spontaneous vomiting and accumulation of fluids in the blood vessels can result in obstruction of the respiratory pathway, abnormally rapid heart rate and impairment of liver and kidney. Shock and respiratory arrest also occur although the severity of cardiovascular and respiratory depression is not comparable with that produced by barbiturate overdose.

Processing Impurities in Clandestine Drugs

The well-established toxic effects produced by some reagents and solvents have not been reported as an abuse consequence of clandestine drugs commonly available on the illicit market. Apart from a recent report on acute lead poisoning in users of illicitly produced methamphetamine (Alcott, 1987), the acute and chronic intoxications hitherto reported mainly concern domestic, industry, and medical practice accidents or voluntary administration in suicide and homicide cases.

The use of commercial solvents as a means of achieving an intoxicated state and the widespread abuse of inhalants, such as aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, fluorocarbons, aliphatic nitrites, ketones, esters, alcohols, glycols, ethers and gases are not relevant to the subject in question (organ toxicity). The changeable traces of chemicals sporadically reported in cocaine, heroin (below listed) and synthetic clandestine drug seizures are closely tied to variable and inefficient manufacturing processes, and significant toxicological effects resulting from short or long-term abuse have not been induced.

Cocaine

Precursors: Acetonedicarboxylic acid; Benzoic anhydride; Benzoyl chloride; Coca leaves; 2,5-Dimethoxytetrahydrofuran; 2,5-Diethoxytetrahydrofuran; Dimethyl-1,3-acetonedicarboxylate; Dimethyl carbonate; Dimethyl beta-ketoglutarate; Furan; beta-Ketoglutaric Acid; Methylamine; Methylamine hydrochloride; Pyrrole;

Reagents: Acetic acid; Acetic anhydride; Ammonia (gas); Ammonium chloride; Ammonium hydroxide; Barium carbonate; Bromine, Calcium carbonate; Disodium phosphate; Hydroxylamine hydrochloride; Mercury; Nitrogen; Oxalic acid; Potassium permanganate; Raney Nickel; Sodium (metal); Sodium amalgam; Sodium bicarbonate; Sodium carbonate; Sodium hydroxide; Sodium methoxide; Sodium nitrite; Sodium phosphate dibasic; Sodium sulfate anhydrous; Sulfuric acid;

Solvents: Acetone; Benzene; Chloroform; Ethanol; Ethyl ether; Kerosene; Methanol; Petroleum ether; Xylene.

Heroin

Precursors: Acetic anhydride; Morphine; Opium;

Reagents: Calcium carbonate; Calcium hydroxide; Charcoal; Hydrochloric acid; Sodium bicarbonate; Sodium carbonate.

Solvents: Chloroform; Ethanol; Ethyl ether.

References

Davies, D.M. *Texbook of Adverse Drug Reactions,* Oxford Medical Publication, New York, 1985.

Pradhan, S.N., Dutta, S.N., *Drug Abuse. Clinical and Basic Aspects.* The C.V. Mosby Company, St. Louis, 1977.

Cox, C.T., Jacobs, M.R., LeBlanc, A.E., Marshman, J.A., Jacobs, M.R., and Fehr, K., *Drugs and Drug Abuse. A Reference Text.* Alcoholism and Drug Addiction Research Foundation, Toronto, 1987.

Jaffe, J.H., Drug Addiction and Drug Abuse, in *Pharmacological Basis of Therapeutics,* A.G. Gilman, L.S. Goodman, and A. Gilman (Eds), MacMillan, New York, 1980.

Strassman, R.J., Adverse Reactions to Psychedelic Drugs, *J. Nerv. Ment. Disease,* 172: 577, 1984.

Fauman, M.A. and Fauman, B.J., The psychiatric aspects of chronic phencyclidine use: a study of chronic PCP users, in *Phencyclidine (PCP) Abuse: An Appraisal,* R.C. Peterson and R.C. Stillman (Eds), 66–118, NIDA Research Monograph 21, Rockville, MD, 1978.

Lerner, S.E., and Burns, R.S., Phencyclidine use among youth: history, epidemiology and acute and chronic intoxication, in *Phencyclidine (PCP) Abuse: An Appraisal,* R.C. Peterson and R.C. Stillman (Eds), 66–118, NIDA Research Monograph 21, Rockville, MD., 1978.

Aptekar, R.G., Possible effects of LSD, *N. Engl. J. Med.,* 283, 765, 1970.

Dumars, K.W., Parenteral drug usage effects upon chromosomes of progeny. *Pediatrics,* 47, 1037, 1971.

Logan, J.W., Neurological aspects of hallucinogenic drugs. In Friedlander W.J. (ed.), *Advances in Neurology,* vol. 13, Raven Press, New York, 1975.

Schatz, H., and Mendelblatt, F., Solar retinopathy from sun-gazing under the influence of LSD, *Br. J. Opthalmol.* 57, 270, 1973.

Blanck, R.R., Singleton, P.T., and Bedynek, J.L., Cardiorespiratory complications of intravenous drug abuse. *Med. Ann. D.C.* 42, 559, 1973.

Felner, J.M., Schlant, R.C., and Hurst, J.W., Cardiovascular complications of drug abuse, *J. Med. Assoc. Georgia* 63, 299, 1974.

Citron, B.P., Halper, M., McCarron, M., and others, Necrotizing angiitis associated with drug abuse, *N. Engl. J. Med.* 283, 1003, 1970.

Halper, M., and Citron, B.P., Necrotizing angiitis associated with drug abuse. *Am. J. Roentgenal* 111, 663, 1971.

Foster, J.B., Clinical features of some miscellaneous neuromuscular disorders in J.N. Walton (ed.), *Disease of voluntary muscle,* Churchill Livingstone, Edinburgh, 1974.

Blain, P.G., and Lane, R.J.M., Drugs and muscle. *Adv. Drug React. Ac. Pois. Rev.* 2, 1, 1983.

Blain, P.G., Adverse effects of drugs on skeletal muscle. *Adv. Drug React. Bull.* 104, 384, 1984.

Lundh, H., and Tunving, K., An extrapyramidal choreiform syndrome caused by amphetamine addiction. *J. Neurol. Neurosurg. Psychiatry,* 44, 728, 1981.

Levin, J.N., Amphetamine ingestion with biliary atresia, *J. Pediatr.* 79, 130, 1971.

Goodman, S.J., and Becker, D.P., Intracranial hemmorrhage associated with amphetamine abuse, *J.A.M.A.* 212, 480, 1970.

Lipski, J., Stimmel, B., Donoso, E., The effect of heroin and multiple drug abuse on the electrocardiogram, *Am. Heart J.* 86, 663, 1973.

Lindel, T.D., Porter, J.M., Langstron, C., Intra-Arterial injections of oral medications, *N. Engl. J. Med.* 287, 1132, 1972.

Besser, G.M., Bulter, P.W.P., Landon, J., Rees, L., Influence of amphetamines on plasma corticosteroid and growth hormone levels in man, *Br. Med. J.* IV, 529, 1969.

Kendrick, W.C., Hull, A.R., Knochel, J.P., Rhabdomyolysis and shock after intravenous amphetamine administration, *Ann. Intern. Med.* 86, 381, 1977.

Davis, L.E., Kalousek, G., Rubenstein, E., Hepatitis associated with illicit use of intravenous methamphetamine, *Pub. Health Rep.,* 85, 809, 1970.

Tuazon, C.U., Cardella, T.A., Sheagren, J.N., Staphylococcal endocarditis in parenteral drug abusers: source of the organism *Ann. Intern. Med.* 82, 788, 1975.

Wilson, P., and Schild, H.O., *Applied Pharmacology,* Churchill Livingstone, London, 1968.

Di Gugno, F., Perec, C.J., Tocci, A.A., Salivary secretion and dental caries experience in drug addicts. *Arch. Oral. Biol.* 26, 363, 1981.

Zalis, E.G., and Parmley, L.F., Fatal amphetamine poisoning, *Arch. Intern. Med.* 112, 822, 1963.

Jaffe, J.H., Martin, W.R., Narcotic analgesics and antagonists, in Goodman, L.S. and Gilman, A. (eds), *The Pharmacological Basis of Therapeutics, MacMillan Publishing,* New York, 1975.

Langston, J.W., and Ballard, P.A., Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, *N.E. J. Med.* 309, 310, 1983.

Davidson, S.I., Reports of ocular adverse reactions, *Trans. Ophthalmol. Soc. U.K.* 93, 495, 1973.

Pinkus, N.B., Skin eruption in drug-induced coma, *Med. J. Aust.* 2, 886, 1971.

Alcott, III J.V., Barnhart, R.A., Mooney, L.A., Acute lead poisoning in two users of illicit methamphetamine, *JAMA,* 258, 24, 1987.

BLANK PAGE

Behavioral Toxicity of Phencyclidine

Paul Luisada, M.D.

Thirty years ago American medical researchers developed a totally new kind of anaesthetic, an intravenous drug which produced surgical levels of anaesthesia without loss of consciousness. Phencyclidine (PCP) or 1-(1-phenylcyclohexyl) piperidine had the additional advantage that it tended to raise blood pressure during surgery rather than lower it. After some deliberation, a new pharmacologic category was created for the drug, it was called a cataleptoid anaesthetic. It was so named because animals it was tested on became docile and immobile and it permitted surgery without pain and without loss of consciousness.

Twenty-five years ago, PCP's short career as a revolutionary anaesthetic ended because too many experimental subjects developed a variety of serious behavioral abnormalities after surgery. These included agitation, assaultiveness, and suicidal thoughts.

Psychiatrists and psychologists then studied PCP's effects in normal volunteers who were subjected to most of the available psychological tests and test situations while under its influence. Most of these apparently normal experimental subjects were found to display psychological test patterns indistinguishable from those of psychotic schizophrenics. A few of these volunteers also became morbid and suicidal. PCP is still the only drug which can produce "schizophrenia" on demand in most apparently normal subjects.

This was the birth of PCP, a drug which was observed from the beginning to affect different animal species in strikingly different ways; cats became catatonic, but rats became ferocious. When it was first used in humans, its effects on different individuals were also strikingly variable; all experienced anaesthesia, but some became violent, others serene. Because of this, the drug's original trade name was Sernyl, and its first street name was "the Peace Pill".

Three decades later, PCP is the street drug best known for its ability to cause violent behavior in users. PCP's street names have continued to multiply for fifteen years, and the diversity of these names reflects the variability of its effects. PCP's names also reflect the paradoxical ways it changes human behavior; at the present time it may be purchased from dealers by asking for either "Love Boat" or "Killer Weed".

Characteristics and Effects of PCP

How can a single drug have such apparently contradictory effects? PCP is different from most other drugs because its effects depend greatly on the unique but individual sensitivity of each user. There is no simple way to describe PCP's behavioral effects, and no way of predicting its effects on an individual before it is taken.

Recent studies have suggested that a better category for it is a sympathomimetic anaesthetic. It has been shown that one end of the pretzel-shaped PCP molecule has sympathomimetic actions in the brain similar to those of amphetamine or cocaine, while the other end has anaesthetic effects like those of morphine. If PCP is considered in this way, as a single drug which is somewhat like a simultaneous injection of speed (methamphetamine), cocaine and heroin, its behavioral effects become easier to understand.

PCP's sympathomimetic effects can be euphoric, dysphoric or psychotic. Whether a given user experiences a euphoric, dysphoric or psychotic response depends on his individual biochemistry. Most users experience a mixture of these effects, and for the majority of users the predominent effect is euphoria.

A user with a euphoric response to PCP has subjective feelings of euphoria and well-being. There is an enhanced sense of control and power, and a sense of omnipotence and invulnerability. Objectively, these individuals show increased alertness, almost hyper-alertness, and an increase in motor activity. They feel unusually strong, and they are because of some direct effects of the drug on the muscles. These individuals also show increased risk-taking behavior, increased aggressiveness and sometimes irritability, paranoia and assaultiveness.

A smaller proportion of users experience the dysphoric response. Subjectively, their thoughts show a morbid preoccupation, their predominant mood is depression, and their hyper-alertness is in the service of paranoid ideas. Objectively, they may be extremely anxious or irritable and withdrawn. They may engage in behavior which is self-mutilating, suicidal or assaultive.

A few PCP users experience the psychotic response. Subjectively, there are auditory and occasionally visual hallucinations, the formation of delusions which may be paranoid and are often bizarre. Their thoughts become disorganized, their attention span brief. Objectively, speech becomes disorganized with loosening of associations, blocking and formal thought disorder. Behavior and dress may become bizarre. Agitation, with assaultiveness or destructive behavior may occur in the presence of others, but isolation and the reduction of stimulation have a calming effect.

Although the euphoric and dysphoric responses to PCP usually last several hours, which is about as long as the individual remains intoxicated, the psychotic reaction usually persists for several days, and usually becomes more severe over the first two or three days. Individuals with PCP psychoses usually require psychiatric hospitalization. Those with prior histories of psychotic or schizophrenic illness are especially vulnerable to the long-lasting PCP psychosis.

The anaesthetic effect of PCP is experienced by all users, but its intensity is dependent on the dose. Subjectively, there is a feeling of numbness, warmth and sometimes floating, in addition to insensitivity to pain and cold. Objectively, there is apparent indifference to physical pain, and a tendency to undress even in the coldest weather.

Among abused drugs in the United States, PCP is without equal in what Burns and Lerner have termed its "behavioral toxicity". That is instead of damaging the user's body through physical illness or chemical toxicity, PCP induces behavior which is dangerous not only to the user, but also to those near him. PCP is distinct from all other drugs in this respect.

It is important to emphasize that PCP does not produce violent behavior in all users, or even in a majority of them. The behavior PCP produces in an individual in an expression of that individual's unique reaction to the drug, and cannot be predicted in advance. However, the particular behavioral response produced in an individual user usually occurs again the next time the drug is administered. Thus, the behavioral response is a characteristic of the user, and not the drug.

Although violent reactions occur in a minority of users, if PCP use becomes widespread in a population, the number of violent incidents will increase, because a larger number of sensitive individuals with this response pattern become exposed to the drug.

Dangerous behavior from PCP use falls into three categories:

1. Accidents due to impaired judgement.
2. Violence towards others.
3. Violence the user directs towards himself.

The profound impairment of judgement which occurs in the PCP user makes him significantly more prone to accidental injury or death than occurs with other drugs. For example, a young woman in California drowned in a swimming pool after keeping herself underwater because she thought she could breathe underwater. A 25 year old man in Washington, D.C. sustained serious injury after deliberately driving his car into a brick wall. He later said that he believed he would simply smash through the wall unscathed.

Accidents and deaths occur primarily to those users who experience the euphoric response to the drug. Their common elements appear to be the unfortunate combination of impaired judgement and euphoric risk-taking with anaesthesia and delusions.

When these effects are combined with the paranoia, irritability, and hyper-alertness experienced by some individuals, violence toward others is sometimes the result. For example, a paranoid user may become violently assaultive towards other people near him if he perceives them as threatening. Several cases have been seen in which armed police officers have been attacked by unarmed users when they approached them for such minor matters as to issue a traffic ticket. The violence extends to family members, such as spouses, parents and children. For example, in 1986, a mother in a Washington suburb murdered her child while under the influence of PCP, believing that the child's crying meant it had become a demon.

The third category of dangerous behavior which may be induced by PCP is deliberately directed at the user himself, and includes self-destructive and self-mutilating acts. The majority of these are suicide attempts. These are most common in individuals who experience a dysphoric reaction to the drug, and the methods of suicide chosen tend to be violent and often painful. Our impression derived from interviewing survivors is that jumping from high places seems to be a particularly attractive method of suicide. For example in the winter of 1986, a 22 year old carpenter walked barefoot for several miles through snow until he reached a 40-foot high railroad signal tower and jumped off. He sustained a fractured skull, leg and back injuries, but was able to crawl along the railroad tracks for some distance until he was found. He was hospitalized for a month recovering from his injuries. Eight months later he was hospitalized in a psychiatric facility by his girlfriend after he used PCP again and told her he was getting a firearm to commit suicide.

Self-mutilating acts are among the most bizarre of the violent acts which have been reported as having occurred under the influence of PCP. The self-mutilation usually consists of amputations of limbs, sense organs, fingers or genitalia with cutting implements. Self-inflicted superficial cuts of the body or extremities appear to be less common.

Chronic PCP users and their behavior were first described by Burns and Lerner. These individual take the drug on a daily (or more frequent) basis for several weeks to several months. The usage pattern in these persons resembles one seen in some amphetamine and cocaine users. Periods of heavy use alternate with periods of abstinence.

During periods of abstinence, PCP users are initially very lethargic and sleep much of the time. They complain of slowed thinking, poor concentration, severe fatigue, and impaired memory. They are nearly always depressed, are often preoccupied with suicidal thoughts, and sometimes make suicide attempts. Cognitive impairment is moderate to severe, and the clinical picture makes these patients appear brain-damaged. Their ability to utilize treatment at this point is severely limited by their cognitive impairment. In the absence of further exposure to PCP, this behavioral syndrome slowly reverses itself spontaneously over an extended period. Whether complete recovery of function occurs after sufficiently prolonged abstinence, and whether antidepressants or dopaminergic drugs will prove to be useful in the treatment of this syndrome, are questions which require further study.

Chronic PCP users are nearly always those who experience a euphoric response to PCP. This seems to be a matter of self-selection, since those with dysphoric or psychotic reactions to the drug are less likely to repeat the experience. During periods of PCP use, chronic users are comparatively functional, but occasionally become psychotic. They seek employment as day laborers, painters, or construction workers. Chronic PCP users in the Washington, D.C. area often sell PCP as a means of ensuring a constant supply of the drug.

Although PCP does not appear to be addictive in the same sense as the opiates, sedatives or alcohol, chronic PCP use shows some similarities. Chronic users gradually increase their daily consumption of the drug, but do not do so beyond a specific limit. If drug use ceases, they enter the depressed, lethargic state described previously, and this can be reversed by resuming drug use. Thus, PCP's withdrawal syndrome is depression and cognitive impairment, and the user continues his drug-taking to avert the withdrawal symptoms. On the other hand, most persons exposed to PCP use the drug intermittently, and only a very small fraction of these become "addicted", if it is appropriate to apply that term to designate the regular daily user.

Conclusion

PCP is a unique synthetic drug because of its "behavioral toxicity". That is: its ability to induce behavior in users which is dangerous not only to the user but also to those around him. The specific behavior is highly variable and is dependent on the user's sensitivity to the drug. The mentally ill are particularly vulnerable to PCP's behavioral toxicity.

If PCP is an example of the effects of the trend toward the increased abuse of synthetic psychoactive substances, then this trend clearly poses a growing danger. The behavioral toxicity of PCP is an object lesson in how drug abuse is now beginning to hurt those in society whose only involvement with the drug user was being physically near him.

Detection, Identification and Epidemiology

238

Developing Indicators of Illicit Use of Analogues and Similar Abuse Patterns

Prof. Dr. med. Wolfram Keup

Summary

Acute and often important changes in the field of substance abuse, such as the appearance of new compounds such as the controlled substance analogues, the occurrence of new combinations, intravenous abuse of oral medications, etc., escape the attention of authorities for too long unless the abuse scene is observed closely and continuously by a capable year-round monitoring system. This is demonstrated with the help of the Substance Abuse Warning System (SAWS) which has been in operation in the Federal Republic of Germany (FRG) for more than 10 years. The characteristics and requirements of such a monitoring system on an international basis for use by global health and other organizations are described. Its application to three examples are described in detail: (1) An epidemic of buprenorphine abuse and addiction, (2) developmental changes of cocaine abuse, and (3) first signs of the abuse of controlled substance analogues ("designer drugs") in the FRG. The global application of a similar monitoring system on a common worldwide basis, needing to be simple, inexpensive, adaptable to developing and industrialized countries, varying educational levels as well as other local conditions, is recommended.

Introduction

Up to 25 years ago there have been worldwide, relatively stable conditions concerning substance abuse; shifts occurred slowly. But since that time profound changes have occurred. Historically, it seems that phases of stability in this respect alternate with others of profound instability, according to some historians in cycles of about 25 years.

In order to effectively counter undesirable changes, reliable information gathering on all possible detail on such changes is of the essence. The appearance of controlled substance analogues, the so-called "designer drugs", has shown that illicit manufacturers have learned to effectively utilize the slowness of national and international authorities in scheduling drugs for their own criminal purposes.

Authorities bear great responsibility; they are restricted by existing laws which to adapt to new requirements take relatively long times. But first of all they need hard facts in order to move this heavy machinery. But hard facts representative for the area usually are not at all available immediately after new patterns or new substances appear, since in the beginning case frequencies are low. Statistically relevant data usually become available only when epidemiological proportions of the particular abuse have already been reached, and when blocking the particular development already has become difficult or even impossible.

To help avoid any such undue delay two changes might be suggested:

1. The spread of legal reaction should be increased, reacting eased, and new legal ways should be explored.

2. Data collection should be improved so that (1) faster registration of changes by continous monitoring of the abuse scene is assured, (2) internationally comparable data is obtained, and (3) animal investigations concerning the abuse potential of medical substances are confirmed, supplemented and, if necessary, corrected.

If properly used, the abuse scene, for medical drugs as well as for street drugs, seems an excellent proving ground, a kind of "voluntary" mass experiment for obtaining practical data on the potential for abuse as well as possible abuse patterns of chemical substances in humans. It was Abraham Wikler who said the ultimate test for the abuse potential of a given new preparation starts only when the preparation is marketed.

Systems responding to such requirements are available in at least a number of countries. The Finnish system and the combination of Client Oriented Data Acquisition Process (CODAP), DAWN and STRIDE in the USA are good examples. The most serious drawnback of the existing systems is that they are not comparable with each other, mostly by differing data bases as well as varying approaches. Some systems are selective and many do not follow the rules of random access. They might favor certain groups, such as street addicts, neglecting medical drugs and the abuse of alcohol. They might record the first and most important substances only which are considered to have caused the emergency room treatment in a case of poisoning. Records may not differentiate between simple abuse and dependence. They might not consider the importance of the substance reported as to the drug career of the addict viewed longitudinally. Often only those substances are recorded to which the user has developed dependence, or those which have been taken during the past six months, etc. In other systems only selected cases are recorded, such as participants in a particular treatment group, college students, prison populations, etc. Many social, medico-psychiatric and cultural aspects are often not considered.

Requirements for Recording Changes

A "perfect system" responding to all the above requirements would be very costly, in money as well as in manpower, so that a compromise ought to be sought. The selected system should be practicable and fast, it should be reasonably inexpensive and impose modest demands on funds and manpower, and it should respond to a number of essential requirements:

1. Data should be collected as closely as possible to the source of information, i.e., the consumer of chemical substances to satisfy the needs of dependence and for "recreational" purposes.

2. A complete record of all substances abused by every person interviewed should be recorded, so that a full picture of the substance abuse career can be drawn. This, as a secondary effect, also has advantages concerning treatment. If less important substances are dropped, the beginning of a particular abuse or pattern of rare types of applications, etc. are surely missed and the early warning function of the recording system is not fully utilized.

3. Methods employed by different institutions in different parts of a country and, if possible, in different countries should be fully comparable and the basic data collection should be standardized in order to allow comparison. To the basic set of standard questions, any additional question of local interest may be added. The same holds for research questions, items of temporary importance, etc. But epidemiological studies by governments, research projects, etc. should use the same set of basic questions so that studies can be compared with each other.

As questions common to all such investigations, the following parameters are offered resulting in a full description of the abuse pattern of the population studied:

—Recording of all substances ever used by each person should include their sequence and duration of abuse.

—The age of the person at the time of onset of abuse for each substance should be determined. Answers to the two questions above allows one to conclude which substance followed which other substance which supports some conclusions on the potential for abuse.

—The main substance group to which the abuser belongs should be determined (alcohol, medical drugs, street drugs). It is essential to know whether a particular medical drug has been abused by a person with alcohol problems (e.g. to boost the alcohol effect) or by a medical drug abuser who also abuses alcohol, etc.

—Abuse pattern as to "trial only", "occasional", "regular" abuse

—Dependence (the definition of which must be standardized)

—Dose level reached for each substance

—Relative preference, resulting in a list of all substances in sequence of overall individual desirability

—Source of supply for each substance (pharmacy, prescribing physician, dealer, etc.)

—Some basic social data together with sex and age

4. Other methodological requirements for a flexible yet reliable re-

cording system are:

—Some systems collect data from all patients treated in facilities for persons with substance abuse throughout the country. Effort and costs are considerable. It is often sufficient to carefully select a representative sample of facilities for the collection of data in a way that they cover North and South, rural and urban areas, wine-growing and beer-drinking areas as well as the different types of institutions such as university clinics, mental hospitals, private hospitals, clinics specializing in the treatment of addicts, etc.

—The selection of the type of contact the selected facilities have with the clients is another important concern. A streetworker with direct contact with the drug scene, a social worker in a shelter for the homeless or a psychologist in an outpatient service for persons with substance abuse problems might be considered to be the best sources of information, since they have close contact with those suffering from dependence. But would the addicts tell them the truth? They rarely will. They have good reasons to fear confrontation with the law and their probation officer or to lose benefits, welfare-payments, etc. Those patients, however, being motivated for treatment and newly admitted to the treatment facility directly from the scene or from skid-row, have good reasons to be as honest as they can be. In our experience, they are not only frank and hardly hide facts but at times must even be watched for a tendency to brag about their many experiences. The best moment of interrogation in the course of a substance abuse career coincides with the availability of well trained and patient investigators among therapists. Thus, indeed, best results are obtained in interviews of newly admitted patients with substance abuse problems in in-patient facilities.

—In addition, it is imperative that the data are collected under all precautions of data protection, are kept anonymous, and do not become part of the patient's case history.

—A representative sample for the country and the area respectively must be collected. The rules of random selection must be followed. It is, however, possible to limit the size of the group interrogated. In most developed Western countries, alcohol problems are so frequent that patients with alcohol dependence are so numerous that their numbers have to be restricted. Randomization then, is achieved only within the groups of patients with alcohol, medical drugs and street drugs, respectively.

—The statistical methods, computer software and hardware should be kept simple in order to assure that developing countries can participate in such a data exchange.

SAWS as an Example of a Fast Recording System

The Substance Abuse Warning System (SAWS) responds to the above-mentioned basic demands (Keup, 1977; 1983). It is cheap, simple, representative for the country (Federal Republic of Germany) and fast in producing results.

Here is how it works:

Approximately 20 collaborating institutions, mostly hospitals for the treatment of patients with substance abuse problems, university psychiatric hospitals, large mental hospitals and also smaller private hospitals, a "pain center", a child psychiatric service, etc. have been selected to be, as a whole, representative for the country as well as possible. On January 1st of each year investigators start interviewing all newly admitted patients with substance abuse problems and continue until they have reached a precalculated quota, determined so as to have them interview their last allotted patient at about the same time of the year. Quotas are calculated by the previous year's admissions. They are preset for each of the main substance groups. A total of 800 to 900 patients are interviewed per year, approximately 300 street drug users, 300 medical drug users and 300 patients with alcohol problems of whom 200 have had experience with medical and/or street drugs as well.

In each institution there is usually only one investigator, many of these are with the system for many years. They have been trained for the job and usually are MD's or psychologists (with a few exceptions), well experienced in the treatment and handling of addicts.

The interview is conducted in the form of a private conversation. The patient's substance abuse career through all substances and preparations ever abused is reproduced on a one "page" questionnaire by the use of codes. The questionnaire is completed by the interviewer during the conversation, contradictions being discussed with the dependent person and excluded from the beginning. For each substance the characteristics shown in Table 1 are obtained.

The figures and letters in Table 1 represent the codes used. Some sociological data and information on previous treatment are collected as well as the sex, age and characteristics classifying the individual in one of four main substance abuse groups: (1) alcohol abuse only, (2) alcohol with additional medical and/or illegal drugs, (3) medical drugs, and (4) illicit street drugs, each possibly in combination with substances of other groups.

In our Central Office those data found to be complete and without contradictions are electronically processed. Detailed profiles are drawn for each substance yearly. The most recent profile is compared to the past profile(s) of the same substance. Any significant deviation causes an alert. The changes are then analyzed in detail and, if need be, additional data are collected by use of a back-up system which is not randomized. It consists of 350 contact addresses of selected practitioners, psychiatric hospitals, university clinics, organizations and facilities for the treatment of addiction problems, some pharmacologists, emergency treatment units and other addressees with direct contact to substance abuse problems in the country. Changes which can be substantiated are reported to the Health Authority of the Government as soon as they appear. Collected

Table 1

Abuse of chemical substances SAWS-System-Main questionnaire

copied from supplementary questionnaire

No.

First psy. treatment ______ years/ ______ mos. ago. Present treatment is the first ( ), sex: ♀( ), ♂( ) ______

Number of treatments due to drug abuse or its sequelae: as out-patient ______, as in-patient ______

Pertinent Group:

	Main substance	solely	also: A	M	D	both
1	Alcohol		▨			
2	Med drugs			▨		
3	Drugs (ill.)				▨	
		1	2	3	4	5

			Sniff-ing		Analgesics					Sedative/ hypnotics					Tranquilizers				Opiates			Morph. relat.			Stimulants					Cannabis				Other Halluc.			Other Substanc				
	Alcohol	Nicotine																	Morphin		Heroin								Cocaine	Hashish			LSD								
A—Names of substances/preparations/ drugs (Name and x)																																									
leave open																																									
B—Year when substance was first used																																									
C—Age at first drug uptake (years)																																									
D—Abuse Pattern: •Sampled (J) •Occasionally abused: past (2a) at time of present therapy start (2b) •Regularly abused: past (3a) at time of present therapy start (3b)																																									
E—How often sampled?																																									
F—How often used occasionally?																																									
G—Duration of regular abuse (months)																																									
H—Frequency of drug taking: monthly/less often (a) up to several times weekly (b) more often/daily (c)																																									
I—Dependence: None (o); past (a), at time of pres. therap. start (b), med. judg't (x)																																									
K—Used: Alone (a), w/friend (b), w/peers (x)																																									
L—Application: orally (o), inhaled (i) inject. (sc, im, iv), supp (s), other (a)																																									
M—Highest permanent daily dose: alcohol estimate in ml ethanol/day; cig (Z); tabl. (T); amp. (A); caps. (K); supp. (S); trip (Tr); drops (Tp); g, mg, L, ml, dl, dg																																									
N—Drug preference: rank (1st, 2nd etc.) not liked (x)																																									
O—Sources of supply: Legal, on market (a) Rp (b), friend (c), dealer (d), theft in pharmacy (e), other (f)																																									
P—Abuse this year? (yes = x)																																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41

See: Comments on attach. quest. (circle)
Domicile at time of admission
with parents ( )1 alone ( )4

Last social status of parents
laborer ( )1 self-employed ( )4
employee ( )2 other ( )5

Last social status of patient
pupil ( )1 laborer ( )4 no job ( )7
apprent. ( )2 employee ( )5

Return to:
Prof. W. Keup
Feldafinger-

244

data, minor changes, as well as improvements, are issued in an Annual Report. Thus the Government has the possibility to obtain and/or request detailed information on any substance or preparation abused in the country.

By the end of 1986 SAWS had collected information on the abuse of 650 legal and illegal substances and preparations, alcohol and nicotine included, of which 58 percent were of minimal and 26 percent of minor importance at that time, but of which 102 (15.7 percent) had reached relevance and statistical significance (with 30–1790 reports per substance).

Samples of Application

The following three examples were selected to demonstrate the applicability of such a monitoring system to the early detection of changes in patterns of abuse:

(1) Buprenorphine (Temgesic), as an example of how such a recording system can follow an upcoming epidemic of abuse finally requiring scheduling of the substance.

(2) Cocaine, as an example of continued recording of the course of a growing menace to the country.

(3) Controlled Substance Analogues, to show how a system like SAWS can follow an early, still very low level problem, a topic which is of particular interest to this meeting.

Buprenorphine (Temgesic)

The thebaine/oripavine analogue and partial agonist buprenorphine was admitted to the pharmaceutical market in the FRG in 1980 in the form of ampules. The sublingual tablets were introduced in May 1983. In February 1982 the first cases of buprenorphine abuse were found and registered in SAWS. Abuse started in the area of Munich, then spread, by a female abuser moving to that town, to Heidelberg and soon all over the country, i.e. within a few months. Mostly, but not solely, street drug users were involved (Keup *et al.,* 1983; Benos, 1983; Keup, 1984).

The most essential data of the abuse pattern of buprenorphine are shown in Table 2.

Table 2 shows results obtained from 272 persons with a personal experience with buprenorphine abuse, with and without dependence. As much as 82.4 percent belonged to the drug scene but only 64.3 percent of this group proved to be dependent on buprenorphine, since most of the users, particularly at the beginning, took the substance as a substitute during a transient lack of money to buy heroin and/or other reasons. In contrast, only 14.7 percent of the persons belonged to the group of medical drug abusers; they showed a higher dependence quota of 87.2 percent, which is well within the range of the quotas of other opiates.

Table 2

Abuse Pattern of Buprenorphine (Temgesic): Dependence

(SAWS-data (Syst. A: N = 169, Syst. B: N = 103)/FRG, 1982–July 30, 1987)

		Dependence							
		No			Yes				
		Trial only	No dependence	Uncertain			No Information	Total	
Main Substance Abuse Group		**N**	**N**	**N**	**N**	**%**	**N**	**N**	**%**
Alcohol (+M/D)		—	—	1	7	*87.5*	—	8	*2.9*
Med. drugs (M)		—	4	1	34	*87.2*	1	40	*14.7*
Street drugs (D)		35	36	4	135	*64.3*	14	224	*82.4*
Total	N	35	40	6	176		15	272	*100.0*
	%	*13.6*	*15.6*	*2.3*	*68.5*				

The manufacturer claimed that buprenorphine abuse simply was the consequence of a temporary heroin shortage at the "scene" and that the addicts would return to heroin as soon as possible. But there were no signs of a general shortage of heroin at that time. Furthermore, from SAWS data, the random sample of 50 persons with a personal experience with both, heroin and buprenorphine, showed the results presented in Table 3.

Table 3

Preference Given to Either Buprenorphine or Heroin By 50 Randomly Selected Street Addicts

(1982-1984; SAWS-data)

Judgment of abusers on preference comparing buprenorphine and heroin	Persons with buprenorphine and heroin experience	
	N	%
HEROIN preferred over buprenorphine	38	76.8
BOTH equally attractive	4	8.0
BUPRENORPHINE preferred over heroin	8	16.0
Total	50	100.0

The 76 percent of the group preferring heroin over buprenorphine did so mostly because they obtained a faster and more intense flash from heroin when injecting it intravenously; in comparison buprenorphine is said to be slower in onset of "flash" and "feeling" but the effect lasts much longer than that of heroin (Keup 1987). Of the group 16 percent preferred buprenorphine over heroin for these reasons. Altogether 24 percent of the group found buprenorphine equal to or better in its desired effect than heroin.

Buprenorphine was scheduled in the FRG in the equivalent of Schedule II of the Psychotropic Convention of 1971 on September 1, 1984. Since that time the number of cases of abuse has dropped to near zero, with the exception of a very few individuals using illicit imports of the substance from Switzerland and other countries.

From Table 4 the further development of abuse since the time of scheduling becomes evident.

To understand Table 4 it is essential to know that in SAWS both past and present abuse are recorded in the two groups with occasional and regular abuse, respectively. Present and regular abuse proved most frequent up to 1984, then diminished to a trickle. In contrast, past abuse, of course, continues to be recorded in the system. Scheduling has been fully effective in preventing this type of dependence.

Table 4

Abuse Pattern of Buprenorphine (Temgesic): Frequency

(SAWS-Syst. A reports only, N=169, FRG, 1982-* July 30, 1987)

	Abuse pattern							
		Occasionally		**Regularly**			**Total**	
Reported in (year)	**Trial only N**	**In the Past N**	**"Present" N**	**In the Past N**	**"Present" N**	**No Info N**	**N**	**%**
1982	1	—	—	1	4	—	6	*3.5*
1983	5	2	2	—	15	1	25	*14.8*
1984	8	5	2	10	15	—	40	*23.7*
9/1/1984 Scheduling in Schedule II/FRG								
1985	5	21	4	19	7	—	56	*33.1*
1986	13	8	—	15	2	—	38	*22.5*
(1987*)	1	2	—	1	—	—	4	*2.4*
N		38	8	46	43			
Total	33	46		89		1	169	*100.0*
%	*19.6*	*27.4*		*.0*				

Table 5

Abuse of Cocaine in the Three Main-Substance Groups

(Alcohol Abuse, Medical Drug and Street Drug Abuse)
Substance Abuse Warning System (SAWS) Data. 1976-Part 1987. (Total Interrogated = 5,612 Persons With Substance Abuse Problems)

	Cocaine Abuse in the Main Substance Abuse Groups								
	Alcohol dependence			**Medical drug dependence**			**Street drug dependence**		
	Persons asked	**Abuse of cocaine**		**Persons asked**	**Abuse of cocaine**		**Persons asked**	**Abuse of cocaine**	
Year	**N**	**N**	**%**	**N**	**N**	**%**	**N**	**N**	**%**
1976–79	803	10	1.2	264	5	1.9	329	124	37.7
1982	268	9	3.4	336	5	1.5	205	98	47.8
1983	249	4	1.6	252	6	2.4	199	137	68.8
1984	264	1	.4	242	3	1.2	204	152	74.5
1985	284	13	4.6	173	6	3.5	338	268	79.3
1986	329	11	3.3	171	2	1.2	324	257	79.3
(1987)*	147	5	3.4	65	2	3.1	165	143	86.7
Total	2012	40	2.0	1343	25	1.9	1416	896	63.3

* = Part of the year only (up to July 31st)

Cocaine

The abuse of cocaine in the FRG has increased gradually during the past years, as in most other European countries. There also was registered a rather steep increase of seizures of illicit cocaine; but a considerable part of it proved to be "transit cocaine", passing through the FRG on its way to other countries. Seizures then are not fully representative of cocaine abuse in the country, on which data can be obtained only at the source, that is the consumers. SAWS in this situation is used as a measuring instrument for trends among users (Keup, 1987).

In this function several parameters of SAWS can be used. Table 5 shows the degree of personal experience with cocaine among the persons interviewed with dependence problems, sudivided into the three main substance groups: alcohol problems, medical drug abuse and illicit street drug abuse.

From these data it is obvious that there is a steep increase of cocaine experience among the street drug users. Of the street addicts, 37.7 percent had had a personal experience with cocaine in 1976–79, but in the first half of 1986, a total of 83.0 percent had such an experience. There are only a very few cocaine-experienced people found in the groups with alcohol and medical drug problems, and there are no significant changes in frequency in these two groups over the years.

Another disquieting finding is the increase of regularly continued cocaine abuse (see Table 6).

There is a decrease of those people who have only tried cocaine and did not continue its abuse in any regular pattern. There also is a decline of those using cocaine occasionally, but in turn there is a distinct increase of those who abuse cocaine regularly. Here, of course, a market is created, a situation which may become dangerous, should the black market price of cocaine decrease. It is well known that competition among dealers presently stiffens, as a consequence of overproduction in South America.

The following data on the actuality of this type of abuse (Table 7) must be viewed jointly with the increase of continuous abuse outlined above.

The two alternatives, "in the past" and "presently", show a distinct shift towards present (at the time of observation), but there might be a trend towards the formation of a plateau beginning with 1983. The conclusion is that cocaine abuse in the FRG shows signs of increasing with growing numbers of current abusers.

Controlled Substance Analogues

The use of chemically altered relatives of scheduled substances maintaining the psychological effect of the parent substance, yet making it possible due to that chemical alteration to avoid prosecution, has start-

Table 6

Changes in the Pattern of Abuse of Cocaine, 1976–1987

(SAWS data; total N = 5612)

Year	Pattern of abuse of cocaine						Total (100%)
	Tried only		Occasionally		Regularly		
	N	%	N	%	N	%	N
1976–79	43	31.4	52	38.0	42	30.6	137
1982	31	28.2	37	33.6	42	38.2	110
1983	34	22.5	49	32.5	68	45.0	151
1984	26	16.7	49	31.4	81	51.9	156
1985	57	19.8	82	28.6	148	51.6	287
1986	47	17.4	55	20.4	168	62.2	270
(1987)*	16	10.7	46	30.7	88	58.7	150
Total	254	20.2	370	29.3	637	50.5	1261

* = part of the year only (N = 377)

Table 7

Pattern of Abuse of Cocaine

Actuality of Abuse at Time of Observation:
"In the Past" = Abuse had Been Terminated Prior to the Interview With the Patient.
"Presently" = Actual Abuse of Cocaine at the Time of Observation.

Year	Actuality of Cocaine abuse: occurring "In the past" %	 "Presently" %	Total (100%) N
1976	90.4	9.6	73
1977	90.0	10.0	40
1978/79	92.0	8.0	25
1982	81.4	18.6	140
1983	64.9	35.1	151
1984	70.5	29.5	156
1985	74.1	25.9	287
1986	75.2	24.8	270
(1987)*	66.0	34.0	150
Total	74.8	25.2	1292

* = Part of the year only (N = 377)

ed to spread from the USA as the country of origin to Canada and a very few other countries. Other countries though should be on the alert; nowhere can present legislation automatically put such substances under narcotic controls. In the FRG the first signs of such abuse have been registered at both, the Federal German Office of Criminal Investigation (Bundeskriminalamt) and the Substance Abuse Warning System (Früh-warn-System).

Table 8 shows the relative frequency of abuse of such illicit substances, together with the abuse of their parent substances as well as a few other related compounds.

3,4-Methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) are recorded in nine and fourteen SAWS reports, respectively. Four persons had experience with both drugs so that a total of 19 persons were involved. Both substances are of research origin (Shulgin et al., 1969) and have meanwhile been scheduled so that they do not exactly belong to the group of "designer drugs". The same holds for 4-bromo-2,5-dimethoxyamphetamine (DOB). Only single reports have been received on the abuse of trimethoxyamphetamine (TMA), related to amphetamine, and of thienylcyclohexylpiperidine (TCP), an analogue of phencyclidine (PCP). There have been no reports on the abuse of analogues of fentanyl and meperidine. Whereas abuse of fentanyl itself is not widespread, the abuse of meperidine has been recorded in 144 cases, starting prior to 1976 and occurring mostly in the

Table 8

Controlled substance analogues and related substances

As Reported to SAWS/FRG 1976–1987 (N = 5449)

Substance name	Reports as of 7/30/87 N	Degree of experience %*	First reported to SAWS Year
Fentanyl & analogues			
Fentanyl	4	*(<0.1)*	1977
analogues	—	—	—
Meperidine & analogues			
Pethidine (Dolantin®)	144	*2.6*	<1976
analogues	—	—	—
Amphetamine derivatives			
(DOM, STP)	32	*0.6*	1976
(DOB)	1	*(<0.1)*	1983
MDMA	14	*0.3*	1985
MDA	9	*(0.2)*	1986
TMA	1	*(<0.1)*	1987
Phencyclidine & analogues			
PCP	8	*(0.1)*	1983
TCP	1	*(<0.1)*	1987
Other substances for comparison:			
LSD-25	1671	*30.7*	<1976
Mescaline	338	*6.2*	<1976
Myristica fragrans	27	*0.5*	1982
DMT	1	*(<0.1)*	1984

*Persons w/abuse of this substance as % of all persons w/substance abuse problems interrogated.

past; its degree of experience was 2.6 percent. All other substances range much lower in frequency.

Some of the other substances introduced in this list of reasons of comparison, such as lysergide (LSD) and mescaline have a much higher abuse frequency in the FRG than the controlled substance analogues; but of course they are "old stock" whereas the "designer drugs" are recent acquisitions. Even the abuse of nutmeg (*Myristica fragrans*; "Jailhouse high") with 27 cases since 1982 and a degree of experience of 0.5 percent is more frequently occurring than MDMA. This is reversed though if the last year only is considered.

In analogy to Table 2 for buprenorphine, Table 9 shows, for the MDA and MDMA patients as well as those four persons who had experience with both these substances, the frequency of dependence tabulated against the three main substance groups.

It is obvious that in the FRG, abusers of these substances exclusively belong to the group of street drug addicts and that dependence is low for both substances; only 3 persons have been reported as being depend-

Table 9

Abuse of MDA and MDMA

Reports to SAWS/Fed. Rep. of Germany.

	MDA Dependence		MDA & MDMA Dependence		MDMA Dependence		TOTAL Dependence	
Main substance abuse group	**No N**	**Yes N**	**No N**	**Yes N**	**No N**	**Yes N**	**No N**	**Yes N**
Alcohol (+ M/D)	—	—	—	—	—	—	—	—
Medic. Drugs (M)	—	—	—	—	—	—	—	—
Street Drugs (D)	4	1	3	1	9	1	16	3
Total	4	1	3	1	9	1	16	3
	5		4		10		19	

Table 10

Abuse of MDA, MDMA/FRG: Pattern of Abuse, Frequency (1985-7/30/87)

Abuse Frequency	**MDA N**	**MDMA N**
Trial only	5	9
Occasionally	2	3
Regularly	2	2
Total	9	14

ent on either one of these substances, so that the data is not yet fully reliable. The low level of dependence is not necessarily entirely related to the abuse potential of the substance because there is no steady supply assured for them.

For the same reason regular abuse is thusly still infrequent (Table 10).

In four incidents only the users were able to obtain enough substance to sustain regular abuse for some time. But the duration of abuse has been recorded in most cases as less than one month.

Fortunately in the FRG no attempts have been undertaken to revive the old idea of using hallucinogens in psychotherapy, as it had been the case with LSD-25, when the abuse potential of this substance was hardly recognized. Such a revival has been attempted with MDMA in Canada (Greer, 1983) and has been favored also by some authors in Switzerland (Baumann, 1986).

The SAWS data are confirmed by the independently collected data of the Federal Office of Criminal Investigation (Bundeskriminalamt, 1987): five incidents of delinquency in connection with the substance, seizure of 28 grams of substance plus 17 capsules and one illicit laboratory seized in connection with MDA since 1985. There were reported 13 cases of substances-related delinquency, the seizure of over four kg. of MDMA and three illicit laboratories closed in connection with MDMA in the same period, and only one case of involvement with TMA. These data are in good congruence with the SAWS data. It shows, that with the help of a random access system designed to be representative for a country it is possible, even with an annual probe of a limited number of cases of abuse, to detect such small scale abuse reliably and early enough for adequate reactions.

The production and abuse of controlled substance analoques is in principle an equally serious problem for European countries as it is for North America. However, it has so far only reached an insignificant level of magnitude compared to other problems, e.g. the abuse of such easily available substances as codeine or dihydrocodeine or the menace of cocaine. It seems presently very possible that this might not change, in parallel to PCP.

For other European countries, according to Interpol data, only a few seizures of controlled substance analogues outside of the FRG have been recorded. Reports on MDMA are included although it is, by origin and legislation, not a "designer drug" in the proper sense (see above):

France:	In several cases MPPP (Meperidine analogue: methylphenylpropionoxypiperidine) has been found. No Laboratories and no other controlled substance analogues found.
Spain:	190 doses of MDMA seized so far. No laboratories found.
Sweden:	180 doses of MDMA have been seized so far. No laboratories found.
Switzerland:	450 doses of MDMA seized so far. No laboratories found.
United Kingdom:	1000 doses of MDMA seized so far. No laboratories found.

Discussion

The use of simple continuous recording systems across borders would be of great interest, not only in the case of controlled substance analogues but also as a basis for scheduling narcotics, measuring abuse patterns of well known illicit drugs, etc. International organizations would be well advised to encourage member nations to set up such systems in their countries following common rules and a common method. Up to now, global decisions often have to be based on fragmentary local information concerning forms of abuse and the abuse scene.

Data on production and criminal activities in connection with substances of abuse are becoming increasingly available worldwide. Laboratory animal testing has been developed to a fine art, yet animal data may show a wide range of interspecies differences. Firm information concerning the species *Homo sapiens*, the consumers of substances and their reactions, however, are scarce. Such data, complex as they are, are monitored effectively in a very few countries only. For that reason decisions often have to be based on spotlight reports, the generalization of which stands on uncertain grounds. There cannot be any doubt that we have to approach closer with our measuring instruments the consumer of habit-forming substances. Indeed, that "voluntary large scale experiment" which goes on all over the world in the scenes of abuse is—as sad as it may be—a great source for obtaining knowledge on substances, substance abuses and abusers. It is a source which, surprisingly, has hardly been tapped systematically, for the benefit of those in danger of becoming dependent and the addicts themselves.

References

Baumann, P.: "Halluzinogen"-unterstuetzte Psychotherapie heute. Schweiz.Aerztereig. 67 (1986) 2202-2205

Bends, J.: Ein Fall von sekundaerer Buprenorphin (Temgesic)—Abhaengigkeit. Nervenarzt 54 (1983) 259-261

Bundeskriminalamt (BKA): Vom BKA in illegalen Market registrierte synthetische Drogan (1985—1.Hj.1987). Stand: 24 July 1987

Greer, G.: A new psychotropic compound and its effects in humans. Santa Fee, N.M. (1983)

Keup, W.: Frusherfassung des Missbrauchsmusters chemischer Substanzen als gesundheitspolitisches Problem. In: FUELGRAFF, G. (edit.): Bewertung von Risiken fuer die Gesundheit, G.Fischer Vlg., Stuttgart New York (1977) 17-32

Keup, W.: Molichkeiten zur Erfassung des Missbrauchsmusters von Medikamenten-Abhaengigkeit. In: WALDMANN, H. (Edit.): Medikamenten-Abhaengigkeit. Akadem. Verlagsges., Wiesbaden (1983) 43-53

Keup, W.: Zentral wirksame Analgetika: Missbrauch als Drogen-Ersatezmittel Dtsch.Aerztebl. 81 (1984) 2561-2566

Keup, W.: Daten zum Cocain-Missbrauch in der Bundesrepublik. Fruehwarnsystem (SAWS)-Bericht Nr.31 to the Government (BGA), FRG (20 Jan. 1987)

Keup, W. Woerz, R. Eckstein, G. Franz, H.: Missbrauchspotential von Buprenorphin. Muench.med.Wschr. 125 (1983) 835-837

Shulgin, A.T. Sargent, T. Naranjo, C.: Structure-activity relationships of one-ring psychotomimetics. Nature 221 (1969) 537-540

Thailand Data Base on Drug Dependence and Illicit Drugs: An Appraisal of Merit for Problem Monitoring and Intervention Planning for Demand Reduction

Vichai Poshyachinda, M.D.

Introduction

The Thailand data base on drug dependence and illicit drugs is comprised of information and statistics from two sources, the regular records of various government agencies and the monitoring systems of the drug dependence treatment population, secondary school students and military recruits. Among the records on illicit drugs, the combined information on seizures of amphetamine-type stimulants and their chemical analyses was the only source for trends on availability and health effects on the users. However, the information does not provide trends on the abusing or dependent population. The monitoring system of the drug dependent treatment population was the most significant single source of trends on the distribution and characteristics of the opiate-dependent population. Statistics from the Central Juvenile Court and the prevalence of opiate use among army and navy recruits provide useful collateral information complementing the monitoring system. The composite information from all data sources, although limited, present fairly good basic information for planning intervention efforts to reduce demand. Given the modest resource investment and the feasibilty for long term continuation, Thailand's current data base has considerable merit. Furthermore, the records of many government agencies have great potential for development into highly useful data bases.

The present communication attempts to describe in brief the data base on drug dependence and illicit drugs that is relevant to changing trends in the nature and extent of the drug dependence problem in Thailand. In referring to the drug dependence status, the opium dependent problem of the hill tribe population is not considered even though it is recognized as significant and closely related to the overall drug dependence situation. Only the dependence data related to the opiates and amphetamine-type stimulants are selected for discussion although many other substances are actively abused and contribute an important share to the national drug dependence problem. The data bases that deal specifically with the law enforcement control of the illicit drug supply are also excluded.

The current data base can be classified into two categories, the regular records of various government agencies and the monitoring systems of specific populations.

Regular Records

There are many government agencies that continuously record information and statistics on the illicit drugs and known drug dependents. Practically all of the data are gathered in the implementation of the intervention programs with the specific purpose being related to the policy of the source agencies.

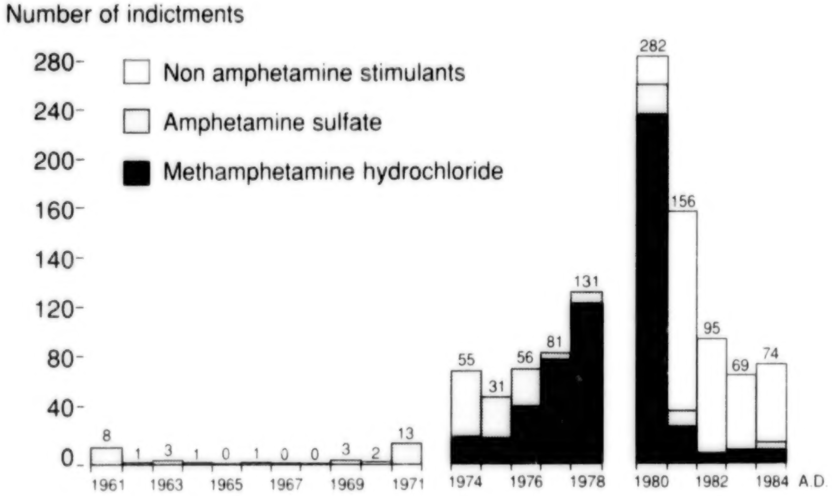
The type of data collected is selected with little concern for monitoring the drug dependence problem. Nevertheless, a large amount of the data are relevant to the monitoring purpose. Examples of some major data sets are illicit drug seizures, chemical analysis of seized drugs, importation and distribution of controlled substances, juvenile and adult convict populations under the Narcotics Law and drug treatment records. The situation on illicit amphetamines as revealed from the regular records is a good example of the value of this group of data sources.

The use of illicit amphetamines among certain groups of the population such as truck and taxi drivers, laborers, night workers and students has been known in Thailand for a long time but the information on the extent of use is lacking. The large drug dependent population that entered treatment services which are widely distributed in the country, do not yield much information. The first case of a drug dependent patient who reported amphetamine as his principal drug appeared in 1972 in the Thanyarak Hospital, the largest government drug dependence treatment center in suburban Bangkok. He was the only case of amphetamine dependence in the annual total of 3,144 cases contained in the hospital records. Since then, fewer cases have been reported each year. During 1979, 1980 and 1981 the respective numbers of amphetamine-dependent patients were 37, 184 and 128 among the annual total of about 7,500 12,000 and 25,000 cases from all licensed treatment centers in the country. Although the numbers are small, a disturbing question relates to a growing population of amphetamine dependents.

Indictments of individuals for possession and distribution of illicit amphetamine-like stimulants indicated an increasing trend in 1971 which continued to rise sharply to a peak in 1980. The illicit drug between 1961–1970 was all amphetamine sulfate. Methamphetamine hydrochloride started replacing amphetamine sulfate in conjunction with the rising number of indictments. In 1980, the peak year for number of indictments, "look-alike" tablets which contained non-amphetamine stimulants appeared for the first time. The share of non-amphetamine stimulant indictments among the total annual indictments continued to increase between 1980–1982, 10.3–95.8 percent against a drop in the total annual number of indictments. Statistics for 1983–1984 demonstrated a resurgence of the amphetamines against a somewhat level total indictment number (Figure 1).

Figure 1

Annual Statistics of Illicit Amphetamine-Type Stimulants Indictments



The drug contents of "look-alike" tablets were rapidly changing. In 1980, when the "look-alike" tablets first appeared, they contained predominantly either caffeine or ephedrine alone. The combination of caffeine and ephedrine appeared for the first time during the last four months of 1980 and rapidly increased to represent almost the total number of stimulant indictments in 1981. The last four months of 1984 saw another shift in the drug content of the "look-alike" tablets. Caffeine and ephedrine as single drug entities seemed to be on the increase (Figure 2).

Until the present, information on the national drug problem related to the amphetamine-type stimulants remained obscure. Less than 100 individuals sought treatment services annually. Among the approximately 10,000 individuals convicted under a narcotic offence, from statistics of the penitentiary system at the end of each year, offences related to amphetamine-type stimulants represented less than one percent. It is obvious that illicit drug seizures and chemical analyses are the only sources of data providing a rudimentary trend of change in the availability of amphetamine-type stimulants.

Records of large numbers of drug dependent individuals belong to the penitentiary system and the drug dependence treatment services. Statistics of the Department of Correction, Ministry of Interior, between 1982–1985 at the end of each year showed the number of prisoners convicted of narcotic offences ranging between 9,959–11,961 persons (16.9–

Figure 2

Drug Content of Look Alike Tablets From Indictment of Amphetamine-Type Stimulants

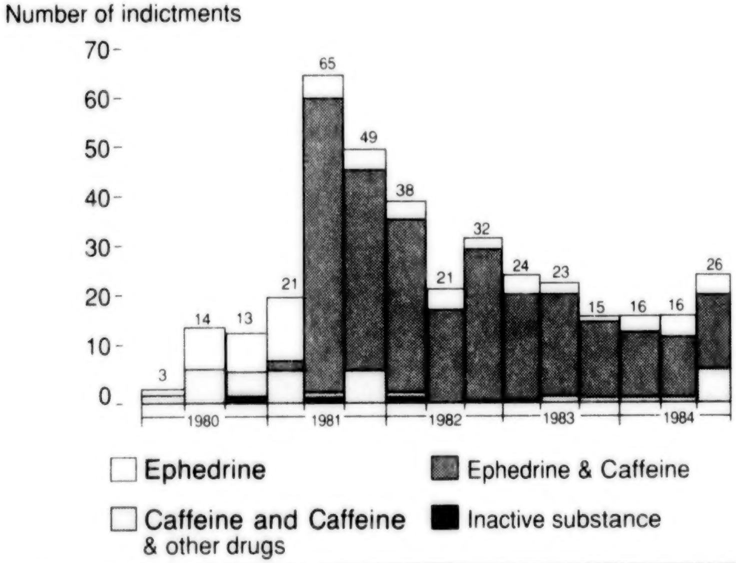
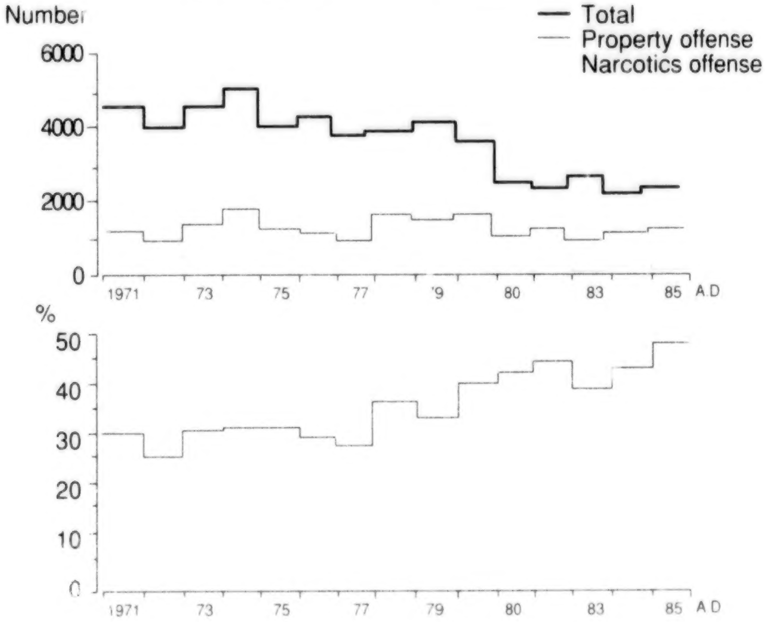


Figure 3

Annual Statistics of Juvenile Convicts of the Central Juvenile Court



19.3 percent of total). The probation cases on narcotics offences of the Central Probation Office, Office of the Judicial Affairs, Ministry of Justice between 1981–1983 amounted to 2,499, 3,920 and 3,686 cases (65.7, 74.2 and 82.6 percent of total), respectively. Annual statistics for juveniles convicted under Narcotic Offenses at the Central Juvenile Court, Ministry of Justice, demonstrated a trend of gradually decreasing numbers and rates between 1975–1985 (Figure 3). From this large pool of a captive drug dependent population, the official statistics revealed little information on the national problem apart from the decreasing trend of juvenile narcotics offenders. The potential to extract data relevant to the national problem because of the direct access to a large target population awaits future development. The data on the drug dependent treatment population are discussed below under Monitoring Systems.

Monitoring Systems

The monitoring systems are new data bases. There are three independent systems with different target populations. One system deals with data from the total drug dependent treatment population. The other two gather data from secondary school students and army and navy recruits. The monitoring system of drug dependent treatment clients is a joint operation of the Treatment Division, Office of Narcotics Control Board, Office of the Prime Minister and the Department of Medical Services, Ministry of Public Health in collaboration with the Institute of Health Research, Chulalongkorn University. The secondary school student monitoring system belongs to the Department of General Education, Ministry of Education. The monitoring of army and navy recruits is under responsible agencies in the Ministry of Defense.

The monitoring system for drug dependent treatment clients is a treatment event reporting system. All drug dependence treatment services are required by regulation of the Ministry of Public Health to report all treatment cases on a common intake form to the Department of Medical Services and the Treatment Division of the Office of Narcotics Control Board. The reportable data include demography, drug use patterns, reasons for drug use and treatment, history of drug dependence treatment, incarceration and relationship with family. The system was launched in 1978. In 1986, there were 92 treatment centers reporting into the system. The treatment centers are scattered widely in all regions of the country; services are provided free of charge; and, the law enforcement control is waived for the treatment client. A fairly large number of the drug dependents voluntarily entered the treatment services. The total number of intakes reported in 1986 was 58,983. The system is designed to elicit epidemiological and management information for planning treatment services. The design does not allow for identification of the person. If there is an identification requirement, a code can be referred back to the treatment center for the identification. For epidemiologic information, the total treatment population in each year was classified into subpopulations according to principal type of drug used during the last thirty days before admission to the treatment services. The specific subpopulation was further grouped according to urbanicity of client residence in Bangkok and provincial regions. Within the urban and rural groups, the population was further classified into the new cases or cases without any drug dependent treatment experience and old cases or cases that had received at least one treatment prior to the present intake. Tables 1 and 2 demonstrate the grouping of the heroin and opium dependent treatment population and the size of the population in the respective groups. Because of the frequent re-entry into the treatment service by the client, the data from new cases is the main resource for trend observation. Heterogenous distribution of heroin and opium users among Bangkok and provincial regions was consistently observed (Figure 4). The heroin users were most prevalent in Bangkok while the opium users predominated in the rural area of the northern and northeastern regions (Tables 1 and 2). The prevalence of new cases per region among the urban and rural areas (Figures 5 and 6) and the geographical distribution of new cases per 100,000 population in each province allowed for a clear trend of changes in the extent of drug dependence (Figures 7 and 8) in highly specific geographical areas of the country. The suggestion of a very gradual increase in the heroin dependent population in Bangkok between 1983–1985 can be observed while in all other provincial regions,

Figure 4

Drug Dependence Treatment Population 1981-1985: Regional Distribution of New Cases of Heroin and Opium Users

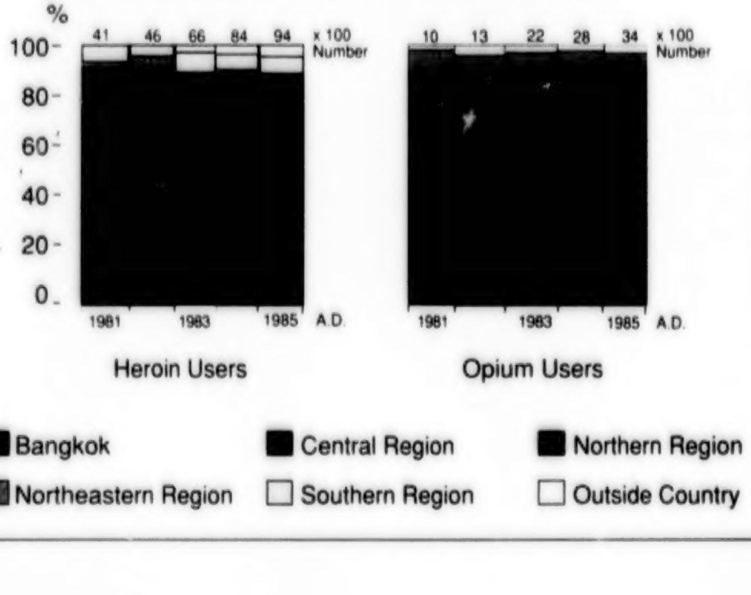


Figure 5

Drug Dependence Treatment Population 1981-1985: Heroin Users' Prevalence of New Cases in Bangkok and Provincial Regions

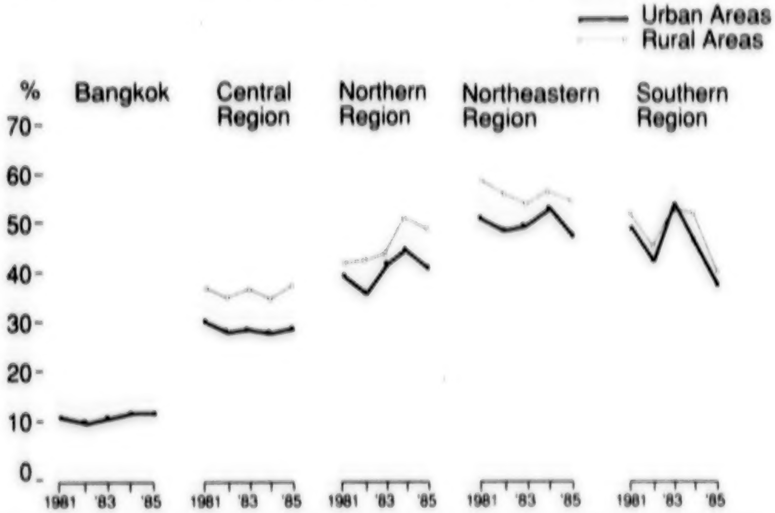


Figure 6

Drug Dependence Treatment Population 1981-1985: Opium Users' Prevalence of New Cases in Bangkok and Provincial Regions

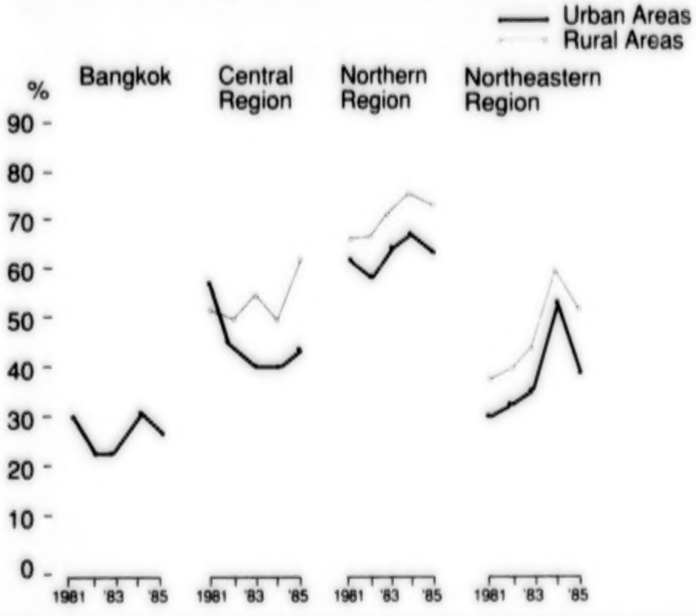


Table 1

Heroin Dependence Treatment Cases Classified by Urbanicity of Residence

	(Number)				
	1981	1982	1983	1984	1985
BANGKOK:					
New cases	1806	2044	2608	3057	3425
Old cases	13720	17159	20281	20754	22112
Total	15526	19203	22889	23811	25537
CENTRAL REGION:					
Urban area:					
New cases	722	780	1064	1243	1620
Old cases	1786	2298	3035	3875	4905
Total	2508	3078	4099	5118	6525
Rural area:					
New cases	609	693	927	1167	1503
Old cases	1133	1386	1681	2401	2711
Total	1742	2079	2608	3568	4214
NORTHERN REGION:					
Urban area:					
New cases	261	294	477	615	538
Old cases	401	581	706	709	739
Total	662	875	1183	1324	1277
Rural area:					
New cases	209	302	393	761	580
Old cases	292	412	453	490	562
Total	501	714	846	1251	1142
NORTHEASTERN REGION:					
Urban area:					
New cases	56	52	107	234	160
Old cases	53	59	113	197	188
Total	109	111	220	431	348
Rural area:					
New cases	59	50	86	141	161
Old cases	33	38	76	96	131
Total	92	88	162	237	292
SOUTHERN REGION:					
Urban area:					
New cases	161	193	446	504	538
Old cases	181	324	423	731	1373
Total	342	517	869	1235	1911
Rural area:					
New cases	199	190	360	422	569
Old cases	192	259	347	429	1138
Total	391	449	707	851	1707

Table 2

Opium Dependence Treatment Cases Classified by Urbanicity of Residence

	(Number)				
	1981	1982	1983	1984	1985
BANGKOK:					
New cases	46	39	37	43	41
Old cases	112	130	124	110	149
Total	158	169	161	153	190
CENTRAL REGION:					
Urban area:					
New cases	46	59	78	48	67
Old cases	37	79	119	72	92
Total	83	138	197	120	159
Rural area:					
New cases	80	113	141	146	219
Old cases	75	115	112	143	140
Total	155	228	253	289	359
NORTHERN REGION:					
Urban area:					
New cases	127	162	302	334	470
Old cases	90	121	153	171	276
Total	217	283	455	505	946
Rural area:					
New cases	546	649	1206	1353	2270
Old cases	274	260	285	283	497
Total	820	909	1491	1636	2767
NORTHEASTERN REGION:					
Urban area:					
New cases	22	40	87	219	63
Old cases	52	86	157	157	103
Total	74	126	244	376	166
Rural area:					
New cases	121	203	273	608	244
Old cases	204	307	338	342	252
Total	325	510	611	950	496
SOUTHERN REGION:					
Urban area:					
New cases	2	17	8	5	4
Old cases	4	4	4	9	6
Total	6	21	12	14	10
Rural area:					
New cases	2	8	11	4	13
Old cases	3	4	1	4	7
Total	5	12	12	8	20

Figure 7

Drug Dependence Treatment Population 1982-1985: Heroin Users' Geographical Distribution in Number of New Cases Per 100,000 Population

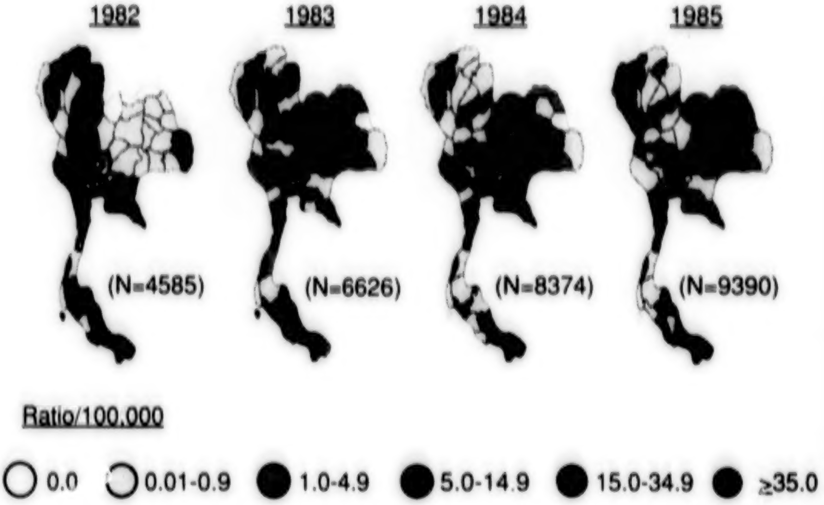


Figure 8

Drug Dependence Treatment Population 1982-1985: Opium Users' Geographical Distribution in Number of New Cases Per 100,000 Population

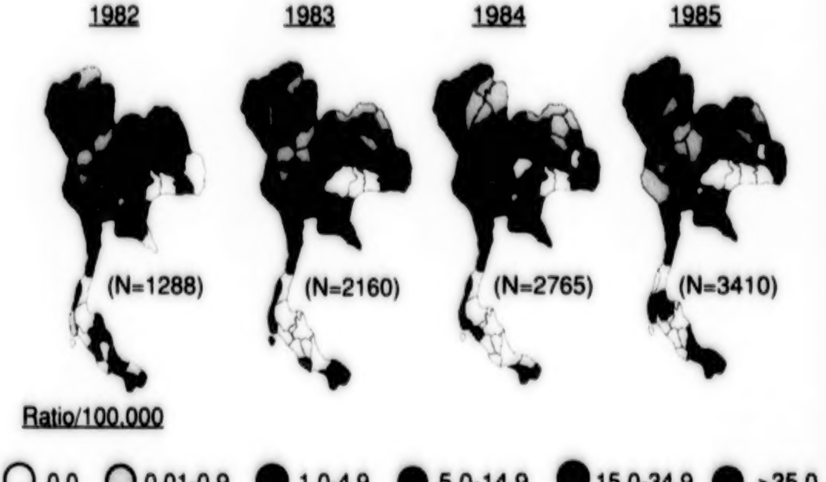
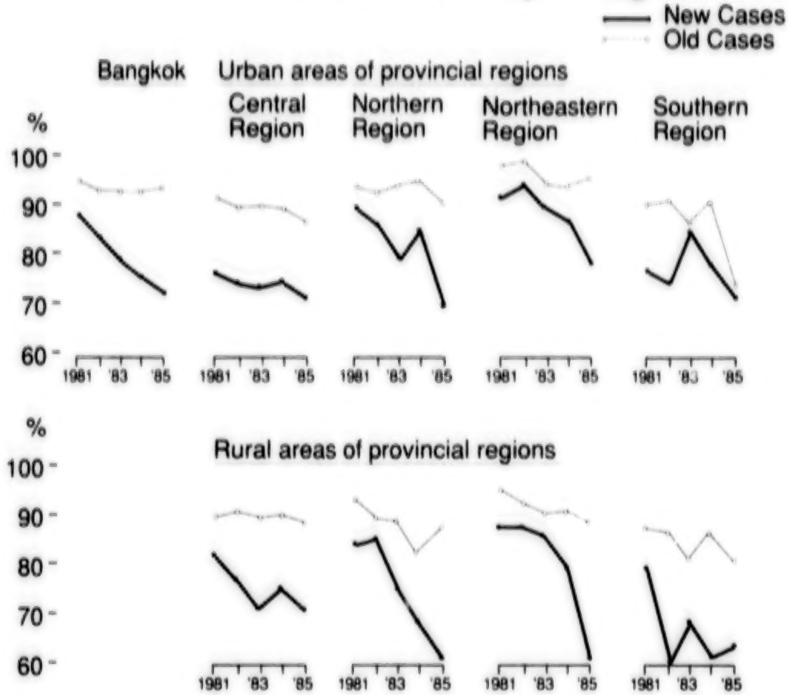


Figure 9

Drug Dependence Treatment Population 1981-1985: Heroin Users' Rate of Intravenous Administration of Principal Drug

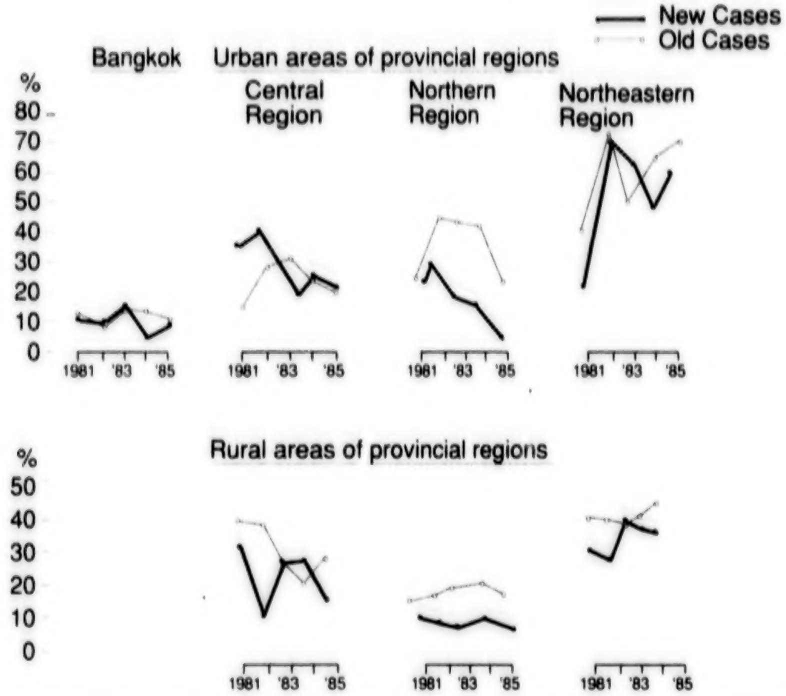


except the central region the trend of decreased heroin dependence in 1985 was noted. Another remarkable trend that the system revealed is the decrease in intravenous administration of heroin and opium in practically all areas (Figures 9 and 10).

To obtain information for management planning, the data were processed by treatment centers which were grouped according to regional location. Provision was made to process the treatment client by treatment center by the same approach for epidemiologic information as already mentioned. The drug dependence treatment centers in Thailand can be divided into three main groups. Each group has, in general, a rather similar treatment approach. The groups are the Buddhist Temple treatment centers which are indigenous institutions, the treatment services of private hospitals and clinics and the treatment services under government agencies. Monitoring the characteristics of clients that voluntarily entered different types of treatment centers demonstrated a unique trend. The Buddhist Temple treatment centers consistently reported nearly 40 percent of their clients using non-opiate drugs while all the rest had no more than 10 percent (Figure 11). The prevalence of new cases

Figure 10

Drug Dependence Treatment Population 1981-1985: Opium Users' Rate of Intravenous Administration of Principal Drug



in the population entering the Buddhist Temple treatment services was much higher than those of others. Furthermore, the prevalence showed a continuously increasing trend between 1983–1985 (Figure 12). The economic status as indicated by the level of income per month of the clients entering the Buddhist Temple treatment center was at the lowest level while the clients entering the private treatment centers was the highest. Expenditures by drug per month also showed the same pattern (Figure 13).

The examples of data from drug dependent treatment population monitoring systems presented so far are perhaps sufficient for the demonstration of the nature of the information yielded.

Secondary school student monitoring is in the early phase of development. The system is actually an annual cross-sectional survey by anonymous self-reported questionnaire administration. The target population is all students in secondary schools under the jurisdiction of the Department of General Education. A common data collection instrument was adopted. The data collected included the demographics, experience in cigarette smoking, alcohol consumption and the use of another nine

Figure 11

Drug Dependence Treatment Population 1983-1985: Distribution by Principal Drug Used During the Last 30 Days Before Admission Classified by Type of Treatment Institution Giving Services

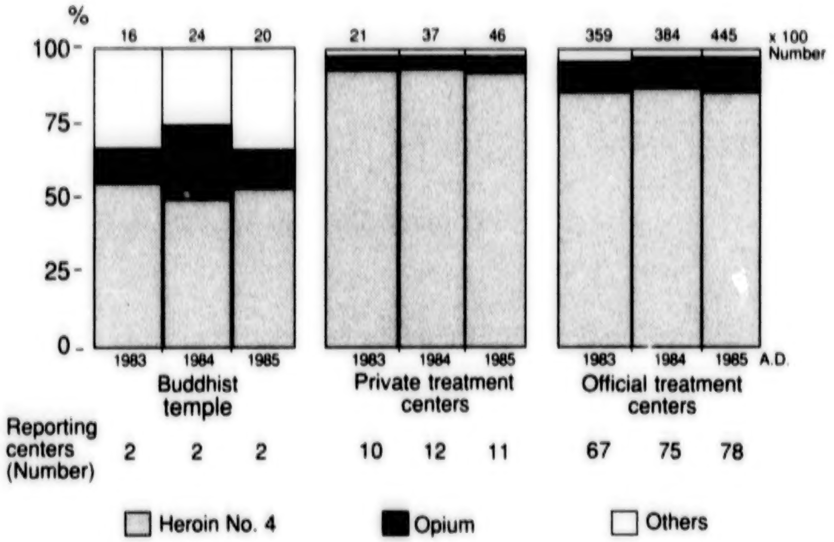


Figure 12

Drug Dependence Treatment Population 1983-1985: Prevalence of New Cases

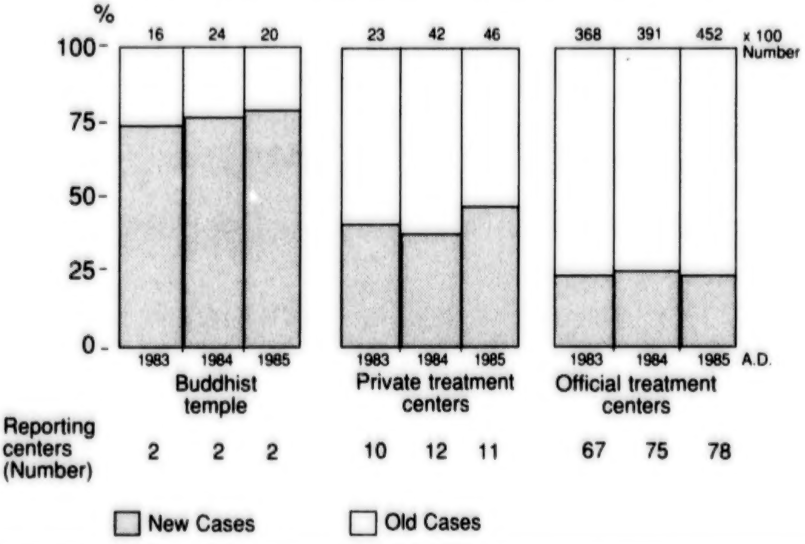
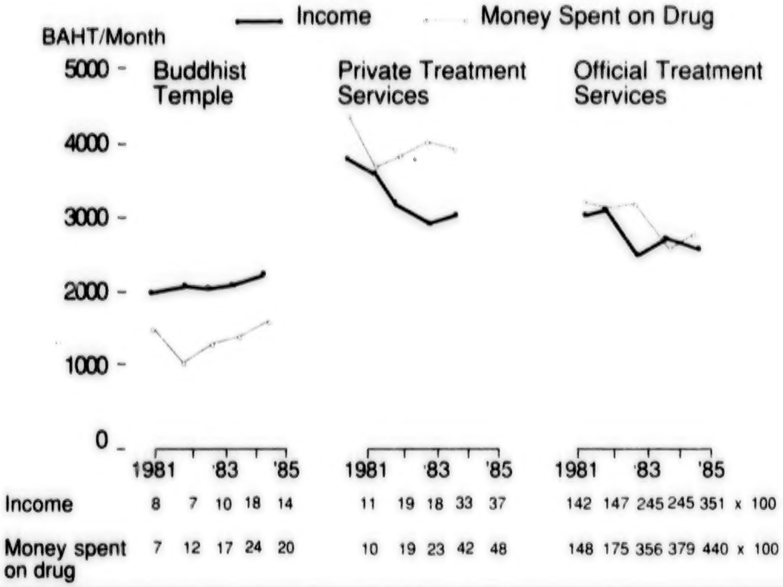


Figure 13

Drug Dependence Treatment Population 1981-1985: Average Income and Money Spent on Drug Classified by Type of Treatment Institutions Giving the Services



drugs commonly experimented with and abused by the student population. Data collection commenced at the beginning of 1986. The results have not yet been released. The Department of General Education plans to expand the data to include other behavorial and social factors related to drug use and delinquency.

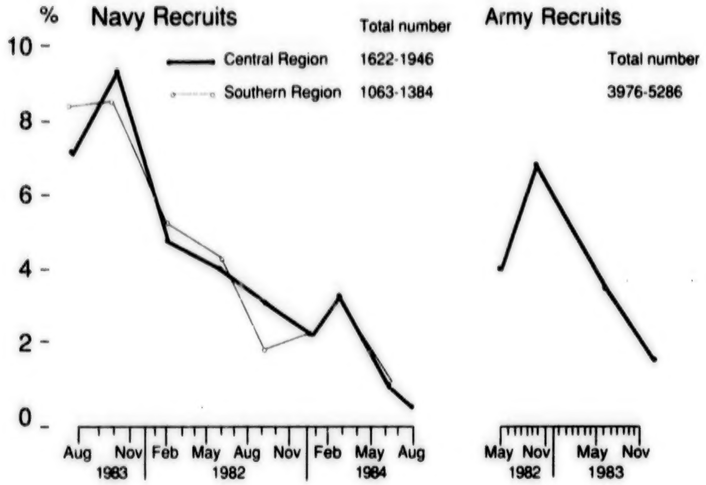
In 1982, the Army and Navy started to monitor opiate dependence among their recruits. Laboratory tests for opiates in urine samples were applied to screen for drug use. Figure 14 demonstrates the trend of a rapid decrease in the prevalence of positive urine tests among other army and navy recruits between 1982–1983.

Monitoring the Drug Dependence Problem

The effectiveness of the data base to monitor the drug dependence problem at the national level requires considerations of four main issues: the amount of the information needed, the sufficiency of their reliability, the timeliness of the availability of the information and long-term continuity. The data bases already discussed have been in operation for a number of years and offer timely information. The available information

Figure 14

Prevalence of Positive Opiate Urinary Test Among Navy and Army Recruits



is related to drugs and the dependent population only. Information on the impact of drug dependence on health and social and economic aspects of the community is lacking because the actual size of the drug dependent population is not evident from the data base. However, with all the data in hand at the moment an estimated number can be systematically generated. A discussion of the reliability of the information from each source is beyond the scope of this communication. It is perhaps sufficient to state that the information obtained thus far from the interpretation of the data does not conflict with known facts. On the contrary, it had been proved on many occasions in the past that subtle changes in the drug dependence problem were indicated by the information long before the Administration and the public were aware of the changes. The minimal data and information already presented are just a fraction of that available.

The monitoring system of the drug dependent treatment population is obviously the most productive in yielding relevant information. This is due solely to the specific design for monitoring at the national level. The balance between long-term operational feasibility and the timely production of sufficiently relevant information was the critical consideration in the designing process. The main approach to the development of the data base was to establish the system in the existing government organizational structure which includes networks of agencies that have immediate access to target populations and the basic expertise and management capability to collect and process the data. It is of great interest to observe the progress of the secondary school student monitoring system. It was designed using the same approach. However, the workload is much greater than the drug dependence treatment monitoring system as it involves data from more than a million subjects. The management and coordination required is phenomenal. Its success will be another major step towards comprehensive coverage of the target population.

Planning of Interventions for Demand Reduction

Planning of intervention programs for demand reduction requires more than information on the drug dependence problem. Effective intervention technology and available resources for implementation are also among the major components needed. At present, there is no concrete knowledge on the effectiveness of either the drug dependence treatment or prevention techniques and programs in operation. Evidence abounds on dependence to substances other than the conventionally known drugs like the opiates, ganja and the amphetamines. Incidental cases of dependent individuals on tranquilizers and organic solvents have appeared in treatment records for more than a decade. Past experience indicates that there are probably many more such cases in the community. In fact, the overall drug dependence problem is most likely growing as the opiate dependence problem is under control. It is clear that the demand reduction intervention effort is currently insufficient. The situation introduces a serious strain on available resources for intervention implementation. That there is more demand for drug dependence treatment services than provided at present is well known. National resources for further expansion of treatment services is already under great economic stress. Information and knowledge that would increase the effectiveness of demand reduction intervention are apparently the priority need.

The information on the drug dependence problem derived from the data base substantiated by technical knowledge on the impact of the problem on health, social and economic components of the community is more sufficient for the planning of the demand intervention than is the information on effective intervention and resources needed. Actually a fair amount of the information is underutilized. However, the situation is not an argument for complacency about the need for improvement. On the contrary, the resources and expertise available are amenable to future progress in data base development.

Concern of Developing Countries in Illicit Manufacture of Controlled Substances and their Analogues

Dr. F.R. Yousuf Fazli

Introduction

The world at large is facing the great challenge of a drug epidemic, but the developing countries, in particular, are being threatened by an alarming sudden spread of new potent substances of abuse. The developing countries are generally unable to tackle the problem due to markedly inadequate resources and competence. Nevertheless, they are very concerned about the introduction of new more potent drugs of abuse.

The drug abuse situation in Pakistan is discussed with respect to its changing pattern resulting from the introduction of heroin and new potent synthetic drugs. The number of new heroin addicts has increased from virtually none in 1979 to about 658,000 in 1986 for a total number of about two million drug addicts in the country. The phenomena of opium cultivation, heroin introduction, government interdiction efforts and related problems are described. Similarly, the medical, chemical and other problems relating to the abuse of synthetic drugs are discussed in view of the danger of the introduction into Pakistan of designer drugs.

Situation in Pakistan

The developing countries have historically always been the recipients of the final clandestine drug product as well as suppliers of the raw materials which are used in their manufacture. Eventually, they also learn manufacturing procedures and can produce the final drug products themselves. In Pakistan, such is the case with the production of narcotics. Opium produced in Pakistan was once converted into heroin in other countries. Now, however, heroin is being clandestinely manufactured within Pakistan as well.

For centuries only indigenous materials like opium and cannabis in the Indo-Pakistan subcontinent were the primary drugs of abuse. However, addiction never emerged as a big social problem. Addiction was limited to the poor, who were mainly an older age group and it did not affect the younger generation. However, with the clandestine manufacture of heroin and the introduction of new potent synthetic narcotic and psychotropic drugs, which were imported for legitimate medical use, the problem of drug abuse has assumed new dimensions. For example, in Pakistan

Figure 1

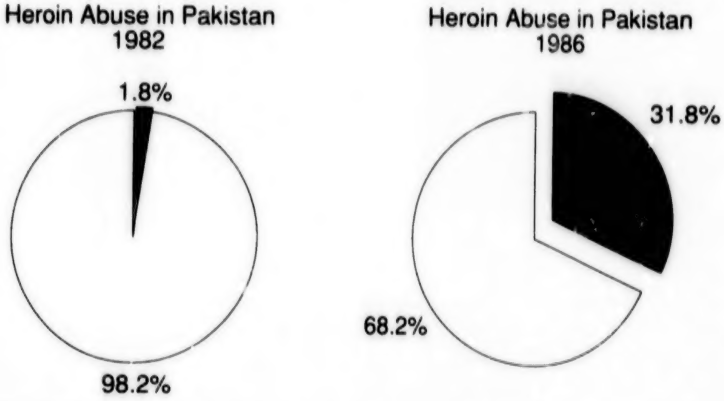
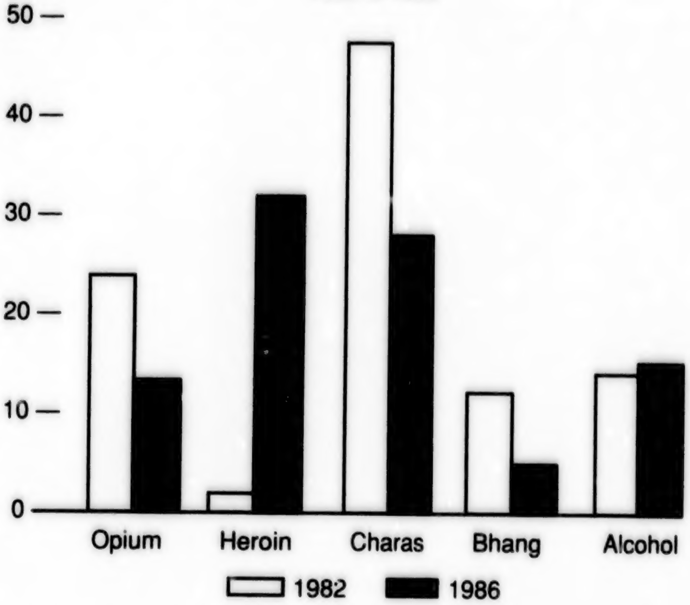


Figure 2

Percentages of Drug Use in Pakistan

1982 & 1986



the abuse of heroin compared to other drugs has increased dramatically in the last five years (Figure 1) with a simultaneous decline in the abuse of opium and cannabis (charas and bhang) products (Figure 2).

The phenomena of abuse of each opium, heroin and the synthetic drugs in Pakistan have their own peculiarities and shall be discussed separately. The former, as defined by Mr. Haislip, represents the first and second phases, whereas the latter represents the third and fourth phases of development in drug abuse.

Opium and Heroin Problem

In Pakistan, poppy is cultivated in the highly underdeveloped tribal belt of Northwest Frontier Province along the Afghan border and in small scattered pockets inland.

In relation to the legal and administrative controls, it is important to understand that in the Northwest Frontier Province, there are presently three categories of land areas: settled, merged and tribal. The governmental controls fully extend to the settled areas whereas they are being gradually extended to the merged areas. However governmental control and administrative infra-structure do not extend to the tribal areas due to tribal freedom, a concept which evolved during the British rule and has been respected by the Government of Pakistan.

The political upheavals of the Western neighborhood of the country with the influx of more than three million Afghan refugees into Pakistan and complete lack of control on their movement has created a situation beyond control.

The drug traffic which found its way from Afghanistan and Iran through Turkey to Europe is now being directed to Pakistan. It has also become risky for traffickers to smuggle heavyweight opium, thus prompting them to set up heroin producing laboratories in Pakistan. Since no control is exercised over the entry of drugs, the Government of Pakistan is making efforts to stop smuggling out of the country through its international ports and other established routes. Sometime back, a sudden ban was also imposed on opium distribution through vending shops. These factors led to the introduction and dramatically fast spread of heroin addiction within the country. Though virtually no heroin addicts were known in 1979, their number in 1987 are estimated to be over 658,000 with a total of two million drug addicts in the country.

This is indeed, a matter of great concern for all and one is forced to ask the question: Is my child safe?

The National Survey on Drug Abuse indicates dangerous trends in Pakistan which may be applicable to many other developing countries. For example

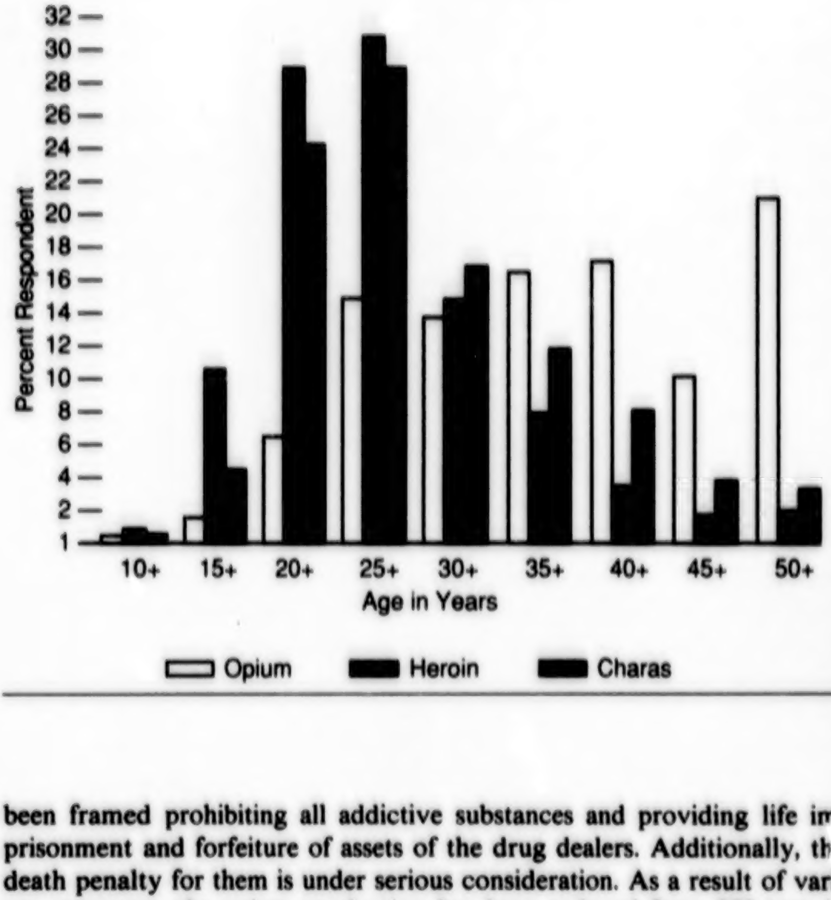
a) Addiction to heroin, opium and charas occurs mostly in younger age groups (Figure 3).

b) With heroin, the urban population is affected more than the rural population with frequency of its relatively highest abuse as compared to other narcotic and psychotropic drugs as shown in Table 1.

Government Measures

The Government of Pakistan has been striving to stop opium cultivation and to destroy heroin producing laboratories. New laws have

Figure 3
Age of Respondents



been framed prohibiting all addictive substances and providing life imprisonment and forfeiture of assets of the drug dealers. Additionally, the death penalty for them is under serious consideration. As a result of various measures, the opium production has been reduced from 800 tons in 1979 to about 130 tons in 1986. With the assistance of United Nations agencies, efforts are continuing to provide substitution of poppy crops with other cash crops, but so far this has been met with limited success due to lack of adequate financial resources. The government has also taken drastic action at times to stop poppy cultivation and trafficking of heroin and other narcotics. They have also led to a serious law and order effort in the country.

In a recent news story, the Government of Pakistan was reported to have bulldozed the poppy fields in the Gadoon district of Frontier Province. This led to a serious crisis involving shooting and killing. A similar drama was also staged at Sohrab Goth, Karachi leading to massacre of hundreds of innocent citizens by the narcotic mafia. But do these measure help to stop the menace of addiction if the sources of drug supply nevertheless continue to exist and produce greater numbers of addicts?

Table 1

The Most Abused Drugs in Pakistan

(As of III Quarter 1986)

Drug	Overall Abusers No.	Urban Abusers No.	Rural Abusers No.	Relative Use by Drug	% of Total Male Adults Using Drugs
Heroin	657392	355421	301971	31.8	2.19
Charas	582024	184176	397848	28.2	1.94
Alcohol	299118	75825	223293	14.5	0.99
Opium	262071	66530	195541	12.7	0.87
Bhang*	125987	25722	100265	6.1	0.42
Tranquilizer	56193	19119	37074	2.7	0.19
Others	8407	41618	42459	4.1	0.28
All Drugs	2066862	768411	1298451	100.1	6.9

*The figures for bhang definitely understate the factual situation. For the purpose of the NSDA, bhang consumption either is reported sporadically or was not included during the hot season.

Financial Problems

For some, the motive behind narcotics trafficking is the lust for money, whereas for others, as in the case of opium cultivation in Pakistan, it is a matter of earning a livelihood. In the N.W. Frontier province of Pakistan, the land, which is the only source of income for the people, is being massively deforested for firewood. The soil thus is suffering from serious erosion with severe siltage of water-ways. Without irrigation, its growing capacity is dropping at a fast rate and becomes unfit to grow anything but the poppy. In order to stop heroin production in Pakistan, it is vital that opium cultivation is stopped completely. This, however, is only possible through development of the area, thus guaranteeing to the people reasonable income, job opportunities and stability including education and health facilities and with that better utilization of land by substitution of crops. A strong legal framework or set up of a battery of treatment and rehabilitation centers will not be able to succeed in controlling drug traffic if drug raw materials continue to be available. What is therefore needed is an overall development of the area requiring resources which are, indeed, lacking for even planning of an appropriate program of this nature. One is thus forced to ask whether we can direct some of the energies and resources being utilized for world destruction to the building of the poor world.

Problem of Synthetic Drugs of Abuse

In Pakistan, codeine, methaqualone, the amphetamines and barbiturates entered the drug scene in the early 1970's. Consequently, all imports for these drugs except phenobarbitone were banned. But methaqualone and amphetamines continue to be available through smuggling from abroad. Currently, methaqualone is also being locally manufactured in clandestine laboratories for domestic consumption. Recently it was discovered that a large quantity of phenobarbitone imported for medical use was being diverted into illicit traffic and was being abused alone as well as in combination with other drugs. Its import had been multiplying by one hundred percent every year which could only be discovered after the import data for the preceding years was collected (Table 2).

Table 2

Import of Phenobarbitone in Pakistan

1984	3150 kg.
1985	6835 kg.
1986	12076 kg.

This year the government has put strict controls on the importation and utilization of phenobarbitone but it has resulted in some shortages for legitimate medical use.

In fact, with the introduction of the potent synthetic drugs in recent years, the abuse of tranquilizers and sedatives has also become a common phenomenon. Addicts, after detoxification, often fall victim to the drugs used for their treatment. These include diazepam and phenobarbitone. Similarly, various mixtures of heroin, methaqualone, tranquilizers, phenobarbitone and antihistamines are also being abused by addicts in Pakistan.

Designer Drugs

The developing countries, due to their many built-in inadequacies are more susceptible to the spread of new addictive substances and thus the newly emerging phenomena of designer drugs is one of their major concerns.

With today's highly advanced knowledge in chemistry when a drug molecule can be relatively easily designed with computer assistance, with desired requirements and also when the raw materials for the manufacture of synthetic products are readily available, the illicit production of designer drugs has become easily possible. Indeed, they have been encountered in some industrialized countries. They have not yet been introduced in the developing countries perhaps due to the ready availability of other narcotic and psychotropic drugs at comparatively low prices. However, the developing countries feel more threatened by the existence of the designer drugs because they create special problems for the doctors, chemists and law enforcement agencies.

a) Medical Problems

Apart from their toxic impurities due to production lacking quality control, the extremely high potency of some of the designer drugs poses major health risks. Minute doses of these drugs produce the desired effect. Unaware of the drug's potency and impurities, administration by the addicts may lead to serious harm and permanent disabilities. This will add to the medical problems of already inadequate health services of the country.

For the treatment of addicts in Pakistan, for example, a few treatment centers have been established with the assistance of United Nations support. But so far, there is virtually no program for the rehabilitation of detoxified patients, thus leading to high relapse rates.

In the recent past, there has been sporadic growth of treatment centers in the private sector. On the other hand, with the increasing use of mixtures of heroin with other unknown substances, detoxification is becoming more and more difficult. In some cases, deaths have been reported during the withdrawal process.

b) Legal Problems

Regarding legal problems, the situation in most developing countries is somewhat different from those of industrialized countries. The former may have all the laws or, for that matter, be able to promulgate new laws, but it is their implementation which is always wanting. The administrative infra-structure within developing countries is ineffective with many built-in weaknesses.

c) Distribution Problems

The sale and distribution of medicines is another area where control is very loose in many developing countries. In Pakistan, for example, there are more than twenty thousand chemist shops which are being run by not well informed pharmacists, a legacy of the past. They may sell any drug without a doctor's prescription even against legal requirements. In the government sector, the concept of proper hospital pharmacy is also non-existent.

d) Education Problems

There is almost complete ignorance on the part of the general public of the critical dimensions of the drug abuse problem. The public is not aware of the value of intellectual and emotional resistance to the temptation of drug abuse.

e) Chemistry and Pharmacology Problems

Currently, a number of addictive substances including synthetic narcotic and psychotropic drugs are being smuggled into developing countries. The drugs, however, escape control measures due to their misleading labelling or by use of synonyms which are not known to the regulatory agencies. Detailed specifications for chemical identification and qualitative and quantitative analysis of such controlled substances are also not readily available to them. Specifications are available mainly for those materials which have been in use for medical purposes and thus effective control is not possible as envisaged. The unavailability of adequate specifications for these substances has also led to confusion in the collection of data and interpretation of legal issues pertaining to the entities to be controlled.

Occasionally controlled substances have also been claimed to have indications not indicative of their addictive properties. This has led to the necessity for delineating clear-cut detailed pharmacological specifications for all the drugs in order to provide assistance to the regulatory agencies. The question of proper chemical and pharmacological nomenclature of narcotic and psychotropic substances has never intrigued the health authorities so much as today with the introduction of "designer drugs" which can be more than a thousand times as potent as morphine and yet may be as legal as candy.

Introduction of controlled substance analogues in some parts of the world poses an even more serious threat to the developing countries, in particular, because adequate resources to control even the known substances of abuse do not exist. The means to identify or check the entry of such substances into the country or for that matter, their trafficking and abuse when their nomenclature is unknown are not available. The capability for testing and analyzing of the drugs by customs and within the country is limited. Laboratories are not adequately equipped with analytical methodology, instrumentation and reference standards to detect, identify or analyze all known narcotic or psychotropic drugs, not to mention the new designer drugs.

Similarly sensitive methods for detection and quantification of low concentrations of substances in body fluids are also not available. Trained manpower for handling these activities is also wanting. Research facilities are virtually non-existent as compared to those in advanced countries. The role of clinical pharmacology and toxicology is another area not yet developed in the developing countries.

Need for Assistance to the Developing Countries

The developing countries are characterized by their relative lack of knowledge, resources and ability to apply control measures. Therefore, they need to be provided assistance by national and international agencies which are in a position to do so to enhance their capacity and capabilities to face not only the new threats of designer drugs but also to tackle the general problem of drug abuse. The contributions of various international agencies are noteworthy. For example, the World Health Organization has done a commendable job in detailing specifications for many such known products particularly those which are in medicinal use. Yet the complexity of the issue and its serious nature demands more vigorous efforts to draw chemical and pharmacological specifications for all known narcotic and psychotropic substances including recognized analogues. The United Nations Fund for Drug Abuse Control has been providing funds to assist countries in their programs of drug abuse control but a lot more is needed to achieve satisfactory results.

Common Problem

If the problem of designer drugs has not been experienced in some countries, it does not mean that it is not their problem. If it is not their problem today, it will be so tomorrow. Heroin was not a problem of Pakistan yesterday but now it is more than its problem. Similarly, designer drugs are a common problem for all of us today and we must make concerted efforts to deal with it together since the trade of illicit drugs has also been well-organized and evenly knit, all over.

Let us hope that through the joint efforts of DEA and WHO, this meeting will culminate with recommendations which will help tackle the problem of controlled substances and meet this new challenge and threat of "designer drugs."

Reference

1. National Survey on Drug Abuse in Pakistan, P.N.C.B., Islamabad (1987).

BLANK PAGE

The Abuse of Illicit Substances in Greece

Dr. Meni Malliori

Considerable information concerning the nature, trends and causal factors contributing to substance use has been accumulated in recent years by means of biological/psychiatric, psychological and socio-anthropological approaches.

During the ten year period, 1973–1983, rapid changes in the drug scene in Greece were empirically observed. Drug use, mainly among youth, became a political issue and exposure through mass-media caused considerable public concern. The need for epidemiological data in order to measure the extent of the problem and develop relevant and efficient preventive programs became evident.

At the beginning of 1983 the Department of Psychiatry, Athens University Medical School, carried out a multidimensional epidemiological study which was sponsored by the Ministry of Youth.

The study included survey of four population sub-groups:

1. A nationwide population survey consisting of a sample of 4,300 individuals, stratified into three groups: 12–17, 18–24, and 25–64 years of age. The individuals were from 57 different geographical areas throughout Greece.

2. A nationwide student population survey consisting of a sample of 11,058 students aged 14–18 years from 96 different schools throughout Greece.

3. A student population survey of Greek immigrants, living in Munich, Federal Republic of Germany, consisting of 1,300 students aged 14–18 years. The students were from all the Greek schools in Munich.

4. A longitudinal cohort study of drug addicts consisting of addicts who were in prison during the survey.

The following is a synopsis of the most important findings of the 1983 survey:

1. Overall illicit drug use in Greece is a real problem affecting all the age groups which were included in the study.

2. Retrospective analysis of the study data showed that there has been a significant decrease in the mean age of drug users during the last ten years.

3. The number of drug users was lower in rural areas in comparison with drug users in urban areas.

4. A very small number of users were under treatment; most users faced punishment instead of treatment.

The above findings in connection with the general state concern led to changes in Greece's drug law which became effective in August 1987.

In the early 1980's the ideological and political approach to the drug problem began to change. Prior to 1980, punishment was the only reponse to any drug abuse problem and any kind of disagreement didn't influence this attitude. The Greek Government recognized the need for new legislation. Policy-makers, criminologists, lawyers, doctors, journalists, political youth organizations and the public were involved in the formulation of the new legislation.

The main characteristics of the new law are compulsory or voluntary treatment programs for drug users and more severe sentences for any person who is convicted of advertising, trafficking or selling illicit drugs.

Members of five Ministries comprise a Committee which is responsible for prevention, treatment and rehabilitation. The money from the penalties for dealers and traffickers will be used to support preventive and treatment programs. The drug addict who successfully completes a treatment and rehabilitation program will have the opportunity to receive a clean police record.

Treatment is seen as one of several ways of controlling the demand for illicit drugs since it should reduce the number of people abusing such substances. The Minister of Health-Welfare and Social Security has the government authority to establish or allow the establishment of non-governmental therapeutic facilities or other institutions for prevention, treatment, and rehabilitation.

It is obvious that in Greece there exists a unique opportunity to evaluate the effectiveness of new legislative approaches, if the above described survey is repeated after a period of two or three years.

The new law should be examined to determine whether it is likley to serve the future needs of treatment programs as they develop over the coming years. The establishment of modern, efficient and comprehensive systems of data collection, storage and analysis are recommended. It is our duty to determine whether the new legislation will succeed in transforming the existing criminal justice system into one which includes prevention, treatment and rehabilitation alternatives.

It is hoped that the new policy will control the supply of illicit drugs and will reduce their demand by programs for primary prevention as well as for treatment and rehabilitation. It relies on both common sense and ethical standards that are fundamentally opposed to the slavery of the mind imposed by the consumptions of dependence-producing drugs.

We welcome the responsibility to inform other countries about the result of our efforts.

Legislation, Law Enforcement and Legal Problems

284-A

Investigative Techniques of Controlled Substance Cases

Raymond J. McKinnon

The term "Dangerous Drugs" is one utilized by DEA to describe all controlled substances other than opiates, cocaine, or cannabis. It includes, but is certainly not limited to controlled substance analogues. Actually, substances such as methamphetamine, amphetamine, lysergide (LSD) and phencyclidine (PCP) are much more commonly encountered in the United States.

The techniques used in investigating all "Dangerous Drugs" cases including the analogs, are basically the same. While the number of dangerous drug cases exceeds 500 annually, the number of analog cases are only a handful per year.

DEA would rarely target a "dangerous drugs" violator without targeting the clandestine laboratory used to produce the substance in question. Resource limitations on manpower, funding, prosecutors and court time dictate that DEA may no longer purchase evidence from illicit venders unless there is a likelihood of immobilizing the laboratory and thereby removing a source of drugs from the streets.

Although the "street corner pusher" is certainly a menace to society and deserves to be removed, he also is easily and immediately replaced by another with little impact on drug availability. DEA must target beyond this seller to the clandestine lab operator. Here hopefully DEA can have some impact on the problem.

In pursuing a dangerous drugs investigation DEA utilizes its ingenuity to outmaneuver the lab operator. Many of the techniques used are basic to all criminal investigations, some specific to narcotics investigations and a few unique only to a particular case. The investigator is limited only by his own imagination.

Some of the common techniques used by DEA in attacking the clandestine laboratory problem are as follows:

Tracking of Precursors

All clandestine laboratory operators must use a number of precursors, solvents and other ingredients to manufacture illicit substances. The idea of following these substances to the scene of the crime is unique to laboratory investigations.

When DEA looked closely at the feasibility of tracking precursors it was quickly apparent that there were too many chemicals involved to take a shotgun approach. Clandestine laboratory operators use a variety of formulas to obtain the same finished product and they tend to stay away from "controlled chemicals" (those that have any legal controls placed on their distribution such as phenyl-2-propanone (P2P)).

DEA established a special enforcement operation (SEO) called "Operation Origination" to design a strategy to locate illicit laboratories by tracking precursors.

First, the most highly abused dangerous drugs were identified. Then it was decided to select a single precursor for each drug on which to concentrate. A consideration in this selection was limited commercial use for the precursor and one whose restriction would not hinder the legitimate chemical industry.

The following list was developed:

Controlled Substance	**Precursor**
Methamphetamine	Phenyl-2-propanone
Amphetamine	Phenylacetic acid
Methamphetamine	Ephedrine
Phencyclidine (PCP)	Piperidine
Methaqualone	Anthranilic acid
Lysergide (LSD)	Ergotamine tartrate

The next step was to establish a dialogue with the chemical manufacturers in order to begin tracking. As expected, the manufacturers were willing to fully cooperate in an attempt to fight the drug problem as long as such cooperation did not impede their legitimate business. The movement of our selected precursors was plotted and the next phase was begun. Meanwhile, continuing liaison would be maintained with the manufacturer.

In this phase, we identified selected wholesalers of the precursors. This selection was based on geographic location, accessibility to the clandestine laboratory operators and cooperation with DEA. Through this relationship DEA was able to develop purchasing patterns unique to the clandestine laboratory operator such as the type and quantity of chemicals purchased, cash sales, and prior business dealing with the chemical suppliers.

Many of these wholesalers worked closely with DEA to provide information and assistance. This included providing access to records and telephone tips on customers and pick-ups.

When this technique was first established it worked exceptionally well. Cooperation was good and the laboratory operators were unaware of how they were being located. Surveillance back to a laboratory site began at the chemical supply house with the assistance of the legitimate businessman. As time went on, the laboratory operators started to realize that their vulnerable point was at the chemical supplier.

The laboratory operators, therefore, modified their methods and DEA found it necessary to make a corresponding adjustment. They used cash sales and unexpected pick-up times which required DEA to extend its hours of surveillance. They used drop-off points to leave the precursor until surveillance ended. DEA countered by use of electronic tracking devices. They took evasive action often leaving the chemical supplier and DEA used aerial surveillance.

At this point, the clandestine laboratory operator was attempting to defeat cooperative efforts with chemical wholesalers, by seeking out new distributors, which may not be cooperative with the Government.

DEA countered with another investigative technique aimed at both tracking precursors to the laboratory site and identifying laboratory operators; DEA established a number of chemical wholesale outlets, that is, "storefront operations" on its own.

The "storefronts" are "sting" operations which sell only those chemicals, equipment and apparatus used in illicit drug production. The operation indicates to its customers that it can be trusted and that it is in business for a quick profit. The "storefront" supposedly looks the other way as the clandestine laboratory operator obtains the necessary chemicals and equipment. Many good investigations have been borne out of the DEA storefront operations.

Unfortunately, at the same time actual "outlaw chemical houses" have emerged. These companies realized tremendous potential profits in selling exclusively to illicit laboratory operators at inflated prices. As they stocked no control substances, inspection by DEA was made impossible; they handled only those precursors needed in the manufacture of "street drugs", thereby reducing their own inventory costs.

These "outlaw houses" have certain other distinguishing features including that they are also involved in legitimate commerce. They operate overtly, pay all required taxes and have the necessary licenses. Therefore, they exude an air of respectability. They frequently expound the opinion "we sell legitimate chemicals and are not responsibile for their use." Additionally, they are uncooperative with law enforcement officials.

Today the vast majority of clandestine laboratory operators purchase their precursors from these "outlaw chemical houses". The results of this switch are twofold.

Firstly, DEA's program with legitimate wholesalers has been reduced considerably due to a lack of recent successes. Secondly, DEA has begun a new phase of "Operation Origination" which targets the "outlaw chemical house" itself.

The object of this operation is an attempt to remove readily available sources of precursors and to turn the chemical supply house operators into witnesses against the laboratory operators or vice versa, as the situation dictates.

The easiest way to immobilize these businesses is to include them in the criminal charges of conspiracy to manufacture illicit drugs.

An example of DEA's success "Operation Origination" is that in the last quarter, four companies have been immobilized, their operators arrested and all company assets valued at $6,800,000 seized.

The technique of tracking precursors and laboratory equipment continues.

Informants

Another very common investigative technique in clandestine laboratory cases is the utilization of informants.

As the name implies, these are human sources of information that are normally involved either directly in or on the fringes of the criminal activity. Their motivations vary, but in the United States consideration at time of sentencing or non-prosecution are the primary factors. Other common motives are financial reward, revenge, and sometimes the desire to extricate oneself from a difficult situation or criminal environment.

The advantage of utilizing informants is that they represent an integral part of the laboratory operators' world and therefore have developed some degree of trust. They learn confidential information during their association and are frequently able to introduce someone to the law enforcement agent or make a controlled purchase of evidence themselves. The chief disadvantage of an informant, however, is his demonstrated lack of loyalty.

In spite of the obvious dangers and disadvantages of working with an informant, he remains the single most important element or tool in a narcotic investigation. An informant is highly valued and frequently well rewarded for his contributions.

Tips

Unlike informant information, tips on clandestine laboratory activity normally come from uninvolved individuals whose suspicions have been aroused. These tips can be extremely valuable in finalizing an investigation or in uncovering a heretofore unknown laboratory.

Tips are merely bits of information passed on by concerned citizens. They may come in the form of reports of unusual smells, activity or movement. They may be from businesses where items from the laboratory were purchased, from landlords, or very frequently from neighbors.

Usually information from these individuals is limited in scope and cannot be expanded upon by the sources. A good investigator, however, can sometimes take these tips and develop them into a clandestine laboratory seizure.

Victims

Victims of drug use, their friends or relatives can be excellent sources of leads in a clandestine laboratory case. There are numerous drug overdose deaths and hospital admissions attributable to substances produced in illicit laboratories. The frustrations felt by either the victims or those close to them can frequently produce a willingness to cooperate with law enforcement. This cooperation can lead to the location of the laboratory, names and locations of those selling the products, methods of distribution, or maybe just to a better understanding of the drug sub-culture in an area.

Fires and Explosions

In a recent survey in northern California approximately 25% of the clandestine laboratory seizures by DEA during the survey time period resulted from fire or an explosion. The very nature of the precursors and solvents used in clandestine laboratories coupled with the lack of expertise of the clandestine chemist dictates that a significant number of the laboratories will burn or explode. In areas of frequent laboratory activity, DEA has undertaken a training program for firemen, teaching them what to look for during or after a fire and to whom the information is to be reported. Such telltale signs of the existence of a laboratory may then be easily recognizable.

Despite total destruction of a clandestine laboratory from a fire or explosion, it is usually still possible to make a prosecutable case from the remains. Witnesses can place the defendants at the scene and there is frequently some evidence of the presence of a controlled substance. Obviously, good evidence-handling procedures and accurate laboratory analysis are essential.

Undercover work

One of the basic and still most productive methods of investigating a narcotics case, including clandestine laboratory cases, is by way of penetration of an organization in an undercover capacity. The advantages of being on the inside include gaining first-hand knowledge of all activity, being able to control the situation, setting the tempo of the investigation, hand-to-hand purchasing of evidence and having a law enforcement officer as the key witness at the time of trial.

Once successful in an undercover role, the operative is limited only by his imagination in the direction that the investigation would take. The primary goal would be to immobilize and prosecute high echelon violators, and secondarily to remove as many perpetrators as possible.

Conclusions

In 1986 DEA seized 509 illicit clandestine laboratories in the United States. By far the majority of these laboratories were manufacturing methamphetamine (372), followed by amphetamine (67). There were 23 laboratories seized converting cocaine base to cocaine hydrochloride. Fentanyl was manufactured by three laboratories and MDMA by five. Of the total number of laboratories 31.2% occurred in California and 24.6% in Texas. Oregon ranked third with 7.2% and Florida fourth with 4.1%. In conjunction with these laboratory seizures, DEA arrested 2710 defendants.

It has been DEA's experiences that the world of clandestine laboratories is very violent and dangerous. Not only does the investigator face all the normal hazards encountered in routine police work, but he also faces a hostile environment inside the laboratory. Exposure to chemicals and contaminants may prove to be more of a long term problem than the violator.

The violator at the laboratory is frequently in a defensive mode. Unlike other criminals who are normally encountered in a somewhat neutral setting, the laboratory is his territory and he has had time to think about defending it. Booby traps are frequently found in clandestine laboratories. They range from very sophisticated devices to simple bottles of ether rigged to ignite the whole laboratory. Basically all laboratories are protected by firearms and automatic weapons are commonplace. As an example of the violence connected with dangerous drugs, the San Diego Police Department Homicide Squad estimated that last year over 40% of all its homicides were related to methamphetamine.

As the number of illicit laboratories seized increases each year, the number of exposures and injuries to DEA personnel increases. Therefore, DEA has had to adapt to this changing situation and to find ways of protecting its employees. DEA has attempted to increase the specialized skills of laboratory investigators with additional training on laboratory investigations and safety procedures. Along these lines, DEA has formalized procedures at the laboratory site in the safe handling of the evidence and chemicals. DEA has developed and issued "state-of-the-art" safety equipment to those engaged in laboratory raids.

As the popularity of the various illicit drugs apparently continues to grow, so will the efforts being expended by DEA on the investigations of clandestine laboratories.

U.S. Analogue and Chemical Legislation

Gene R. Haislip

The U.S. Congress, in response to a need to reduce the time required for the control of abusable substances, passed legislation giving DEA emergency scheduling authority in the fall of 1984. Beginning in April 1985, DEA used this authority on five occasions to emergency schedule 13 controlled substance analogues. Although the time required for the control of analogues was reduced there was a need for even a quicker response. In October 1986, the Controlled Substance Analogue Enforcement Act was passed. It established as a criminal act the manufacture and distribution of controlled substance analogues intended for human consumption and if such activity was outside the framework of the drug development and approval process. A controlled substance analogue is defined as a substance with a similar chemical structure producing or represented as producing a stimulant, depressant or hallucinogenic effect similar to that of a Schedule I or II controlled substance.

Precursor and essential chemical monitoring legislation has been proposed in the U.S. Congress. The proposed legislation, the "Chemical Diversion and Trafficking Act of 1987", is a comprehensive proposal that would establish a system of sales records, import/export documentation, and purchaser identification over a number of select precursors and essential chemicals. By way of definition, a "precursor chemical" is a substance that may be used in the chemical process of manufacturing controlled substances, which is incorporated into the final product, and is therefore critical to its manufacture and an "essential chemical" is a substance that may be used in the chemical process of manufacturing controlled substances as a solvent, reagent or catalyst.

It would be a criminal offense not to comply with the provisions of this law. The sale of all tabletting and encapsulating equipment would be reported. Exemptions for chemicals available in drug form (e.g., ephedrine) would be provided. It is believed that this is a practical approach not providing for all contingencies but one which provides maximum benefits with limited burdens.

Extent of the Problem

Cocaine, heroin, PCP and amphetamine/methamphetamine are four of the twenty drugs most commonly mentioned in U.S. hospital emergency room drug abuse episodes. They are also either synthetically produced in clandestine laboratories or are produced by illicit processing of plant materials, such as in the case of heroin and cocaine. It is estimated that these four drugs alone accounted for over 106,100 hospital emergency room mentions in 1986. LSD, another clandestinely produced drug, accounted for 2,800 mentions during this period. In the case of all these drugs, traffickers must obtain the various precursor and essential chemicals in order to produce the final product, the abused drug. Clearly clandestine manufacture and processing of drugs of abuse are major U.S. problems.

Since 1980, clandestine drug-producing laboratories have been uncovered by law enforcement officials in Belgium, Bolivia, Brazil, Canada, Colombia, Costa Rica, Denmark, the Dominican Republic, the Federal Republic of Germany, Mexico, the Netherlands, Norway, Panama, the Republic of Korea, Sweden, Taiwan, Thailand, Turkey, Venezuela, the United Kingdom, and the United States. In addition to these nations where illicit drug manufacture occurs, other nations have been implicated in the trafficking of these substances or their chemical precursors. These include the Bahamas, France, Greece, Indonesia, Japan, and the Republic of South Africa.

Laboratories seized in other nations since 1984 were manufacturing heroin, cocaine, methamphetamine, amphetamine, methaqualone, and LSD. PCP availability in nations outside of the United States has also been confirmed.

In the United States, the major drugs of abuse manufactured clandestinely from available industrial chemicals used as precursors are methamphetamine, amphetamine, phencyclidine (PCP), methaqualone, 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), fentanyl, and lysergic acid diethylamide (LSD). In addition, significant quantities of coca paste are processed into cocaine hydrochloride

Summary of Domestic Clandestine Laboratory Seizures

In FY 1986, a total of 509 clandestine laboratories in the United States were seized by DEA and other law enforcement authorities. Of these laboratories, 372 were methamphetamine-producing, 67 were amphetamine-producing and 21 were manufacturing only the Schedule II controlled precursor of methamphetamine and amphetamine, 1-phenyl-2-propanone (P2P). Therefore, a total of 90.4 percent of all seized laboratories in FY 1986 were involved in illicit amphetamine-like stimulant manufacture. Together with the 23 cocaine processing laboratories seized in the United States in FY 1986, stimulants accounted for 94.9 percent of all laboratories seized.

The second most frequently encountered group in the United States was the hallucinogens; they comprised 18 laboratories, or 3.5 percent of the total. The hallucinogens which were clandestinely manufactured included PCP (8 labs), MDA (3 labs), MDMA (5 labs), and LSD (2 labs). The sedative-hypnotic methaqualone was manufactured by four seized laboratories (less than 1 percent). Finally, four narcotic-producing laboratories were also seized in FY 1986; three of the laboratories were manufacturing fentanyl and one was producing heroin.

The total number of seized laboratories, paralleling overall illicit activity, has increased steadily from 197 in FY 1982 to 509 in FY 1986. This represents an increase of 158 percent in four years. Additionally, in the first half of FY 1987, 302 clandestine laboratories were seized.

Current Efforts to Reduce Clandestine Laboratories

The U.S. Drug Enforcement Administration has maintained an active voluntary program with the U.S. chemical industry to identify instances of diversion of precursors and essential chemicals into the illicit market. DEA has also enlisted the cooperation of a number of chemical producing nations to assist in the identification of suspect shipments in international commerce. In addition to voluntary programs, DEA has implemented the provisions of the "Piperidine Reporting" provision of the Psychotropic Substances Act of 1978 (P.L. 95-633). This created a system of mandatory reporting of piperidine sales by the chemical industry, as well as other requirements to curtail diversion of piperidine. While this voluntary cooperative activity and piperidine reporting have produced some successes, the clandestine production of illicit dangerous drugs and the processing of illicit narcotics continue to be major drug abuse problems affecting the United States.

While voluntary precursor and essential chemical programs have been effective in dealing with the problems of clandestine synthesis and processing of drugs of abuse, such programs alone are not an adequate remedy. Scheduling of immediate precursors under the provisions of the Controlled Substances Act might curtail the diversion of these substances into the illicit traffic; however, this would bring with it the burden of extensive record-keeping, security, labeling, production quotas, and other requirements. The challenge the United States is facing today is to develop an effective system of control that will impact on the diversion of precursors and essential chemicals without unduly restricting the legitimate transactions and uses of these chemicals.

Summary of Legislative Needs

1. Clandestinely manufactured dangerous drugs, heroin, and cocaine are major drug abuse problems in the United States.

2. The diversion of precursors and essential chemicals used in clandestine synthesis and processing of illicit drugs is a major contributing factor to the availability of drugs on the illicit market.

3. Past efforts involving voluntary precursor and essential chemical programs have provided limited success in dealing with the problem.

4. Previous legislative efforts, particularly the "piperidine reporting" statute, have provided a strong basis for collecting information on transactions involving piperidine. However, the expansion of a mandatory reporting scheme for the number of precursor and essential chemicals necessary to impact on the problem would be overly burdensome on the chemical industry and the government.

5. The authority to control "immediate precursors" under the same schedule of the CSA as the drug it produces can be an effective tool in reducing diversion. However, this too can result in an excessive burden resulting from required security, reporting, record-keeping, quotas and other provisions of the CSA.

6. Additional authority to curtail the diversion of precursors and essential chemicals will be necessary if an effective law enforcement effort is to be mounted against clandestinely synthesized and processed drugs.

7. This additional authority must temper the needs of the law enforcement community in curtailing the diversion of these chemicals with the need to provide for uninterrupted legitimate use of these chemicals.

8. The "Chemical Diversion and Trafficking Act of 1987" provides for an effective deterrent against the diversion of precursor and essential chemicals while not inhibiting legitimate utilization of these chemicals.

9. The United States Government and other nations must continue their national and international efforts to impact on trafficking in both clandestinely produced drugs and the chemicals used in illicit manufacture and processing.

Misuse of Drugs Enforcement in the United Kingdom

Dr. A.W. Scaplehorn

The misuse of drugs is a matter of great concern to Her Majesty's Government and to people throughout the United Kingdom. It has been the cause of many personal and family tragedies. The Government gives the highest priority to tackling the problem and greatly values the commitment shown by the wide range of groups and individuals who share their concern both nationally and internationally.

There can be no single explanation for the increase in drug misuse and the problem has to be tackled in a variety of ways. In the UK, the Government's strategy is embodied in the booklet published by the Home Office entitled "Tackling Drug Misuse: A Summary of the Government's Strategy." Essentially the problem is being tackled on five major fronts:

—reducing supplies from abroad
—making enforcement even more effective
—strengthening deterrence and tightening domestic controls
—developing prevention
—improving treatment and rehabilitation

Overseeing, coordinating, giving impetus to and reviewing the many measures which give practical effect to the Government's strategy is an interdepartmental Ministerial Group on the Misuse of Drugs under the chairmanship of one of the Home Office Ministers who has special responsibility for drug matters. The Home Office has the lead responsibility for developing and coordinating the implementation and presentation of both the domestic and the international aspects of the Government's strategy for combating drug misuse. It is also responsible in England and Wales (and, in certain respects, Scotland) for the scope, effectiveness, enforcement and administration of the controls in the Misuse of Drugs Act of 1971 and its associated subordinate legislation. Other departments with an active involvement include the Department of Health and Social Security, the Department of Education and Science, the Department of the Environment, the Board of HM Customs and Excise, the Ministry of Defense, the Foreign and Commonwealth Office, the Overseas Department Administration, the three departments of the Scottish Office, the Welsh Office and the Department of Health and Social Security Northern Ireland and the Department of Education Northern Ireland.

The principal legislation concerned with the control of drugs in the United Kingdom is the Misuse of Drugs Act 1971 and the various regulations made under it. Other relevant legislation includes the Medicines

Act 1968 and the Customs and Excise Management Act 1979 and the recently introduced Drugs Trafficking Offenses Act 1986.

The Misuse of Drugs Act 1971

This Act preserved the general pattern of control established by earlier legislation but made more extensive provision for controlling drugs in order to prevent their misuse, and for dealing with social problems connected with their misuse. Flexibility of control is offered, first, by the power to bring a drug under control by Order in Council and, second, by wide powers to make regulations.

The Act established the Advisory Council on the Misuse of Drugs with the task of keeping under review the misuse of drugs in the United Kingdom and of advising Ministers on measures to deal with the social problems caused by such misuse.

It also prohibits the import and export, production and supply and possession of controlled drugs, but enables regulations to be made and/or licenses to be issued to exempt legitimate trade in, and use of, controlled drugs from these provisions.

The Act enables the Home Secretary to give a direction in certain circumstances withdrawing from a doctor, dentist, veterinary surgeon, practitioner, or pharmacist, his authority to prescribe specified controlled drugs, for example.

The principal offenses under the Act are those created by Section 4 (unlawful production and supply), section 5 (unlawful possession, and possession with intent to supply unlawfully), (permitting the use of premises for certain activities in regard to controlled drugs) and Sections 12(6) and 13(3) (contravening a direction of the Home Secretary prohibiting a practitioner from prescribing). Offenses of unlawful import and export (Section 3) are established under the Customs and Excise Management Act 1979 (see below).

The broad principle governing penalties is that the highest penalties related to trafficking in its various forms, and penalties, in general, are graded in accordance with the degree of harm accorded to the particular drug concerned by its place in Class A, B or C of Schedule 2. Thus, the current maximum penalty for trafficking in a Class A drug is life imprisonment. Simple possession of a Class C drug attracts a maximum two years imprisonment.

The drugs listed in Schedule 2 are as follows: Class A includes opium, heroin, methadone, morphine, and other narcotic drugs placed under the strictest control by the United Nations Single Convention on Narcotic Drugs, 1961. It also contains derivatives of cannabis and certain other hallucinogens, such as LSD, and injectable amphetamines, which are controlled under the 1971 Convention on Psychotropic Substances.

Class B includes six opiate drugs, one of them being codeine, which are less strictly controlled under the Single Convention. It also includes cannabis, cannabis resin, six stimulant drugs of the amphetamine group controlled under the 1971 Convention and medium and long-acting barbiturates. Three further 1971 Convention drugs, i.e., glutethimide, lefetamine and pentazocine, are included in Class B by Order in Council (The Misuse of Drugs Act 1971 (Modification) Order 1985 (SI 1985 No 1995) effective 1 April 1986).

Class C contains other drugs in the amphetamine group, some controlled internationally, which, on present experience, are considered to be less dangerous. The Order mentioned above also added 33 tranquilizers of the benzodiazepine group, including diazepam, four sedatives and two appetite suppressants (all 39 drugs are controlled under the 1971 Convention) to Class C effective 1 April 1986.

The Medicines Act 1968

This Act provides for the control of medicinal products and certain other substances and articles through a system of product licenses and clinical trial certificates, and the licensing of firms or persons engaged in the manufacture or assembly of such products or by wholesale dealing in them. The Act also provides that all medicines, except those appearing in a General Sale List, shall be sold only from registered pharmacies and that certain medicines may be supplied only on prescription.

The Customs and Excise Management Act 1979

This Act creates (Sections 50, 68 and 170) various offenses in relation to the importation and exportation of goods contrary to any prohibition or restriction for the time being in force under any enactment with regard to the goods. Schedule I of this Act provides penalties where a smuggling offense involves a drug controlled under the Misuse of Drugs Act 1971. The maximum custodial sentences are the same as those for trafficking offenses under the Misuse of Drugs Act.

The Law Reform (Miscellaneous Provisions) (Scotland) Act 1985

Section 39 of this Act inserts a new section 193B into the Criminal Procedure (Scotland) Act 1975. This section provides that when a court sentences a person to imprisonment for a drug trafficking crime it is to consider the profits likely to have been made by the offender from that crime and impose a fine in addition to the term of imprisonment unless the court considers it inappropriate to do so.

Section 193B of the 1975 Act further provides that where an offender defaults on the payment of such a fine, any term of imprisonment imposed in default will be served consecutively upon the main term of imprisonment or detention imposed with respect to the drug trafficking crime (unless the original sentence is one of imprisonment or detention for life).

For the purposes of this provision a drug trafficking crime is defined in Section 193B(4) of the Criminal Procedure (Scotland) Act 1975 as inserted by Section 39 of the Law Reform (Miscellaneous Provisions) (Scotland) Act 1985.

The Drug Trafficking Offenses Act 1986

This applies to England and Wales and includes measures to strengthen investigative powers and to permit the pre-trial freezing of suspected drug traffickers' assets, backed up on conviction by immediate confiscation of the assets to the value of the entire proceeds made from trafficking.

Enforcement

Enforcement of the legislation is undertaken by the Customs and the police.

There are two principal aspects of customs control. First, there is preventive control by staff at ports, airports, container depots and parcel post depots and on coastal surveillance. Secondly, there is investigation by specialist investigation officers working on information and intelligence gathered from various sources at home and overseas in order to anticipate, target and intercept consignments. There is a close working relationship between the preventive staff and the specialist investigators, each providing invaluable support for the other.

The police operational response is at three broad levels. Uniformed and plain clothes officers deal with offenses involving the individual misuses which arise in the normal course of their duties. The drug squads and CID deal with more serious cases of misuse of drugs and trafficking offenses occurring within the force area. The Regional Crime Squads together with their recently introduced Drug Wings provide a mobile network of experienced detective officers who are able by virtue of their organizational structure, to investigate drug trafficking networks involving more than a single force area and which might stretch across the country. There are also frequent police/Customs joint operations.

Supporting these operational arms is a National Drugs Intelligence Unit (NDIU) to provide both the police and the Customs with nationally coordinated intelligence to aid their efforts to combat the spread of illegal drugs. This non-operational unit is run from New Scotland Yard and is headed by the National Drugs Intelligence Coordinator. Its staff is drawn from officers from police forces throughout the United Kingdom and from Customs Officers. Closely linked to the NDIU is the Drugs Intelligence Laboratory at Aldermaston which receives intelligence from all the UK forensic science laboratories. Details of all cases involving seizures of greater than one gram of heroin, methamphetamine and amphetamine, together with all lysergide (LSD) and cocaine cases and any unusual controlled drugs are transmitted from the forensic science laboratories to Aldermaston and then on to London for intelligence analysis.

Related to this laboratory input is the precursor monitoring program undertaken by the Home Office Drugs Inspectorate and local police forces and coordinated centrally by NDIU.

BLANK PAGE

Drug Law Enforcement in a Developing Country

Prof. Juan Carlos Garcia Fernandez

International Conventions

Argentina has a broad and rich tradition of adherence to international treaties, conventions, and protocols on drug control. This tradition began with the International Opium Convention (Hague) which was signed on January 23, 1912, approved by Resolution No. 16.765 and changed to Law Number 12.912 on December 26, 1947. It was followed by the International Opium Convention (Geneva) signed on February 19, 1925 in Geneva, approved by the Argentine Government by Resolution Number 88125 on August 10, 1936. Other treaties, conventions, and protocols to which Argentina adhered are described below.

The Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs (Geneva, 1931) was approved by the Resolutions previously mentioned (1936) and ratified by the same Law (1947). The Lake Success Protocol (1946) modified the mentioned Conventions and transferred some health related functions of the League of Nations to the World Health Organization (WHO). Argentina joined the Protocol for Limiting and Regulating Cultivations of the Poppy Plant, the Production of International and Wholesale Trade in and Use of Opium (New York, 1953) on December 26, 1957 by Law Resolution No. 16.919.

The Single Convention on Narcotic Drugs (1961), completed in New York on March 30 of that year, was approved by the Government of Argentina on December 13, 1963 by Resolution-Law No. 7672, with some reservations. The Convention on Psychotropic Substances was then signed in Vienna on February 21, 1971.

The Protocol modifying the 1961 Single Convention on Narcotic Drugs, signed in Geneva on March 25, 1972, was ratified by Argentina by Law No.20.419 (September 23, 1976).

Finally, the South American Agreement on Narcotics and Psychotropics, signed in Buenos Aires on April 27, 1973, was ratified by Law No. 21.422 on September 23, 1976.

In accordance with Article 49 of the Single Convention on Narcotic Drugs, 1961, regarding transitional reservations, Argentina reserved the right to permit in part of its territory (Salta, Jujuy and Tucuman Provinces, all of them in Northwest Argentina) coca leaf chewing to satisfy the ancestral habits of the native population and the particularly difficult conditions of the life in those regions (Article 49, paragraph 1(c)).

The Convention requires that "coca leaf chewing must be abolished within twenty-five years from the coming into force of this Convention as provided in paragraph one of Article 41'' (That means 1987) (Article 49, paragraph 2(e)).

According to an internal Resolution (1958), the importation of coca leaves which was 190 tons in 1958, was to be restricted to ten tons per year, so that since 1977 practically no more coca leaves have been licitly imported into Argentina.

Thinking that the seriousness of drug abuse required permanent and consolidated attention from all the countries of South America, these nations held a Plenipotentiary South American Conference on Narcotics and Psychotropic Substances (Buenos Aires, April 25-27, 1973).

In the 16 articles of the conference Agreement the participating nations agreed to hold periodic meetings, to create an institution to coordinate and centralize in each country everything related to drug abuse and control, to give support to scientific investigations, to standardize rules of the countries which signed the Agreement, to give high quality training to security forces, to benefit from information interchange with Interpol, etc. (Buenos Aires, March 27, 1973). Later on, two additional protocols on health sanitary and penal legislation were added.

Article 10 of the Agreement provides a description of the objectives and principles of those present. Article 10: To enforce the necessary regulations to get a close collaboration and an efficient information interchange in everything related to the fight against the illegal use of narcotics and psychotropics, especially with reference to: (a) Illicit traffic control; (b) Illicit traffic suppression; (c) Cooperation between federal security forces; (d) Harmonization between penal and civil laws; (e) Uniformity of administrative regulations on the sale; (f) Prevention of drug abuse; and (g) Treatment and rehabilitation of drug addicts.

The Argentina Republic has been a member of the CICAD (INTERAMERICAN COMMISSION FOR DRUG ABUSE CONTROL) since the FIRST PERIOD OF ORDINARY SESSIONS (April 21-25, 1987).

The RIO DE JANEIRO INTERAMERICAN PROGRAM OF ACTION AGAINST USE, PRODUCTION AND ILLICIT TRAFFIC OF NARCOTICS AND PSYCHOTROPIC SUBSTANCES, establishes the areas in which CICAD activities will develop. Principal fields for CICAD are: (a) Interamerican cooperation; (b) Principal aspects and program priorities; and (c) Relations with United Nations and other subregional organisms.

The program priorities are: (1) demand reduction; (2) supply reduction; (3) organization of a new data bank, and other subjects such as drug abuse prevention; treatment and rehabilitation, and investigation. In the area of supply reduction, law enforcement will focus on production and other important items. The future importance of this international organization is obvious.

National Laws

Health sanitary legislation is chiefly based upon two laws: Law Number 17.818 on Narcotics (July 29, 1968), and later modified by Law Number 18.346 of September 12, 1969 and Law Number 19.303 on Psychotropic Substances (October 11, 1971), later modified by the Law Number 19.678 (June 12, 1972) and Law Number 20.179 (February 22, 1973).

Law Number 17.818 on Narcotics in its general resolutions defines the substances which qualify as "narcotics", establishes quantities that a narcotic substance may be consumed, imported and exported. The rules further regulate home production, home commerce, public expenditures, the fines to infringers, and their prescription.

This law covers all the narcotic substances under control in Argentina in four schedules which are periodically revised.

Resolution Number 81 (January 13, 1958) determined that coca leaf importation for legal consumption was to be reduced. Legal importation of coca leaves decreased from 190 kg. in 1958 to 10 kg. in 1976.

Since the Convention on Psychotropic Substances had not been ratified by the Argentina Republic as of October 1971, the Technical Department of the Public Health Secretary together with the National Institute of Mental Health and the Section on Personal Security of the Federal Police, based on the recommendations of the Economic and Social Council, drafted a law providing for health regulations regarding import control, distribution and the scientific use of psychotropic drugs, and establishing penalties for illicit actions involving some psychotropic substances. These proposals became Law 19.303 on October 11, 1971.

Chapter 1 of Law 19.303 defines psychotropic substances as those included in Schedules I through IV. Subsequent chapters treat other areas including importation, exportation, national preparation, home commerce, retail commerce, shipments, penalties, prescriptions, preventive measures, etc.

Schedules I to IV are not unalterable; on the contrary, they may be periodically modified to reflect the new or changing drugs of abuse in Argentina (for example, as shown by the addition of methaqualone and pentazocine). These substances were scheduled in Argentina before the United Nations Commission on Narcotic Drugs placed them under international control.

Trends concerning psychotropic drug abuse are very well known in Argentina. Many papers have been specifically written regarding this aspect of drug abuse by individuals in intoxication centers, specialized laboratories, and rehabilitation and treatment centers (CENARESO).

It is necessary to closely watch pharmaceutical drugs to be able to follow changes in consumption and to spot the appearance of abuse.

Permanent control under Argentine law made it possible to act quickly in situations like those involving the abuse of pentazocine even before these problems became so serious that international control was necessary. In the case of the benzodiazepines, Argentina, together with other member states, followed an energetic policy that culminated when the Commission on Narcotic Drugs decided by a wide majority to include them (33 benzodiazepines) in Schedule IV of the Convention. Such control means that, at a minimum, a medical prescription must be kept at the pharmacy as a requirement of sale.

Drug abuse was again changing in Argentina. Local statistics showed that out of 173 abusers, 12 percent used dextromethorphan bromohydrate. Therefore, it was decided under Resolution Number 129 of the Ministry of Health and Social Action, that pharmaceutical products containing dextromethorphan bromohydrate may be dispensed only with a maintained record and with accompanying information that at high doses they may produce psychic dependence (This Resolution was supported for similar antecedents as Resolution Number V/18 from ASEP or Resolution from Oriental Republic of Uruguay).

Based on information that out of 447 drug dependent patients, 30.4 percent abused the antitussive Zipeprol, it was decided to include it in the same regime under Resolution Number 129 (February 6, 1982).

Law Number 20.771 filled a void in Argentine law regarding the abuse and control of narcotics. The narcotic substances were defined under several resolutions that began with Number 162.74; 845/75 and 1802/76. Prohibited activities involving specified "narcotics" are enumerated in Article 10 of the Law (Cattani, 1977). Other resolutions to periodically update the law followed those already mentioned.

Law Number 20.771, sanctioned on September 26, 1974, was promulgated on October 3, 1974. The law establishes penalties for those people who are authorized to sell medical substances but dispense them in a manner (quality or quantity) not in accordance with a medical prescription; for those who sow, cultivate or keep seeds capable of germination; for those who produce, extract or prepare narcotics; for physicians who prescribe narcotics for non-therapeutic reasons; for those who facilitate the use of a place for the mentioned activities; for those who keep narcotics even for personal use; for those who try to induce other persons to consume narcotics and for those who use narcotics in public places.

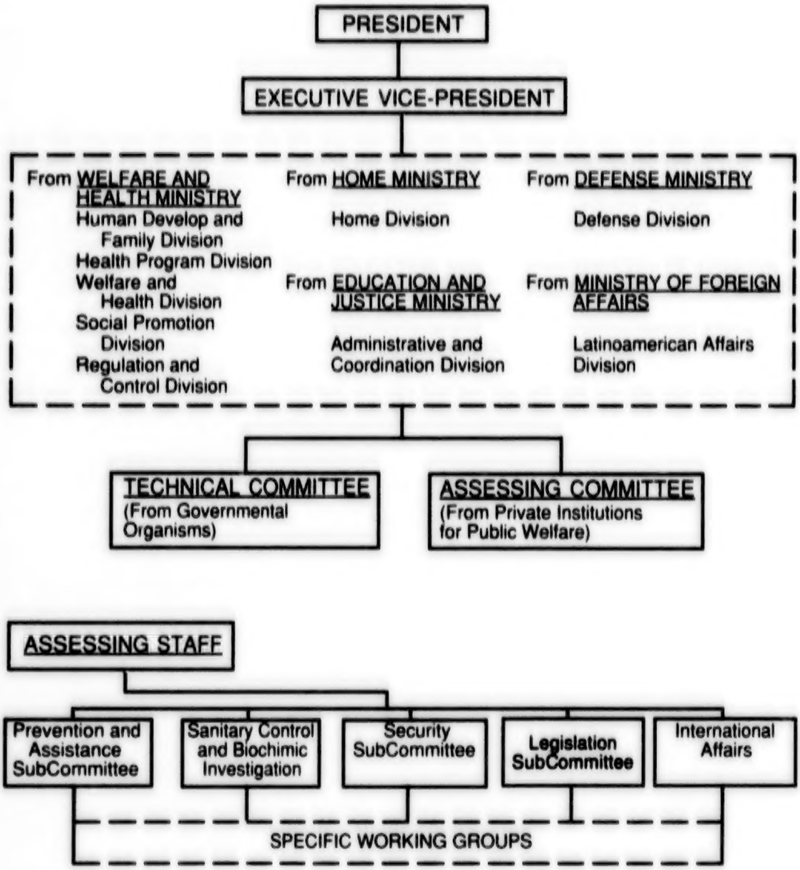
Resolution Number 162 (S.E.S.P.—State Secretary of Public Health) indicates which drugs are scheduled in the last paragraph of Article 77 of the Penal Code. Another article was added to Law Number 20.771 (Article 9 Bis) that establishes immediate incineration of specimens of *Papaver somniferum L.*, *Erythroxylon coca* and *Cannabis sativa L.*

Drug Law Enforcement Institutions

The NATIONAL COMMISSION AGAINST NARCOTRAFFIC AND DRUG ABUSE (CONCONAD) functions in Argentina as a coordinating institution in control of drug abuse. A table of organization is shown below in Figure 1.

The security forces with the specific function of narcotraffic control are the Argentine Federal Police, the Federal Frontiers Police, Federal Coast Guard, Airport Police and the Federal Customs Department. They have a very important function in the detection of traffickers and drug

Figure 1
National Commission Against Narcotraffic and Drug Abuse


PRESIDENT
EXECUTIVE VICE-PRESIDENT
From WELFARE AND HEALTH MINISTRY
Human Develop and Family Division
Health Program Division
Welfare and Health Division
Social Promotion Division
Regulation and Control Division
From HOME MINISTRY
Home Division
From EDUCATION AND JUSTICE MINISTRY
Administrative and Coordination Division
From DEFENSE MINISTRY
Defense Division
From MINISTRY OF FOREIGN AFFAIRS
Latinoamerican Affairs Division
TECHNICAL COMMITTEE
(From Governmental Organisms)
ASSESSING COMMITTEE
(From Private Institutions for Public Welfare)
ASSESSING STAFF
Prevention and Assistance SubCommittee
Sanitary Control and Biochimic Investigation
Security SubCommittee
Legislation SubCommittee
International Affairs
SPECIFIC WORKING GROUPS

smuggling, through the Dangerous Drugs Office.

The Federal Police are directly under the Interior Ministry; the other three Security Forces are under their respective Armed Forces. The Federal Customs Department is under the Ministry of Commerce.

The Federal Police, and the Federal Coast Guard have important laboratories. The Federal Justice Laboratory deals with most of the drug problems while Federal Frontiers Police and Federal Coast Guards also have laboratories which are used according to their needs.

Open and Integrated Information Network for Equipment and Systems Interconnection (Corsunsky)

In supporting establishment of a data bank for the Argentine Police Agreement, CONCONAD led to help in creating the "Open and Integrated Information Network for Equipment and Systems Interconnection."

In January 1987 an agreement was signed by the Argentine Federal Police, the Federal Migrations Department, the Federal Frontiers Police, and the Federal Customs Department, whose aim is to use the data bank to check on persons prior histories.

It is the responsibility of the Federal Judiciary to enforce laws approved by the National Congress, to give opinions on the responsibilities of each case and person, and to apply the corresponding penalties.

Federal Judges have direct jurisdiction in drug related cases, although due to the complexity of some cases (attempted suicide, overdose deaths, etc.), Judges of Criminal Instruction and Sentence may intervene.

The Forensic Medical Body, dependent on the Federal Court of Appeals on Criminal and Correction Actions, has responsibility in many cases of casualties due to drug overdose, suicides, and related accidents. The Buenos Aires Forensic Medical Body is made up of approximately thirty-six forensic doctors who work in pairs. The Dean of the Forensic Medical Body is responsible for the Laboratory on Toxicology and Legal Chemistry which specifically deals with visceral analysis and all types of drugs, both pure drugs as well as those in biological media. The laboratory is under the direction of two forensic chemical experts.

Each province has its own Supreme Court (as does the Nation as a whole), cameras and forensic medical body, with a variable number of components according to its state. Unfortunately, not all of them have a complete forensic medical body.

The data bank previously has produced some interesting statistics for 1986. Drug trafficking cases showed a large increase in 1985, which continued through 1986 (Datos de Policía Federal, 1987) (Figure 2).

As a consequence, an increase in the number of traffickers arrested is also noticed (Figure 3).

Marijuana seizures show a similar profile, with more than a 100 percent increase from 1984 (745,691 g seized in 1984) to 1,553,936 g in 1985. That increase is maintained through 1986 (Figure 4).

Marijuana plant seizures, however, only increased substantially in 1986. It is necessary to keep in mind that according to some earlier statistics only 10 percent of the consumed marijuana in Argentina came from local illicit crops. According to the same statistics, imported marijuana was used in the country. The increase in seizures was not only due to local production, but due to smuggling, specifically through the Northeast border (Figure 5).

There could be several reasons for such increases, particularly since there were no changes in drug legislation. These reasons could be: (1) a

Figure 2

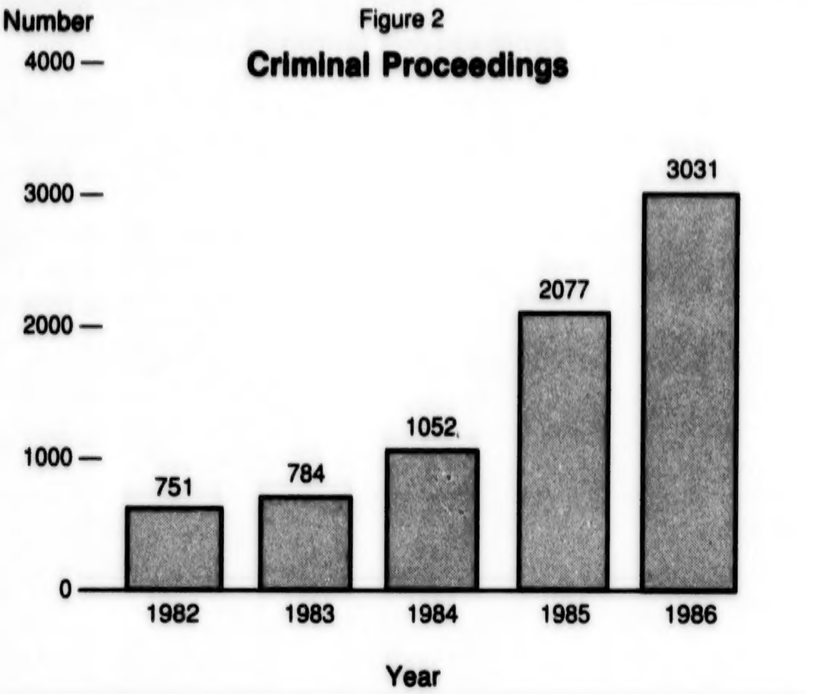
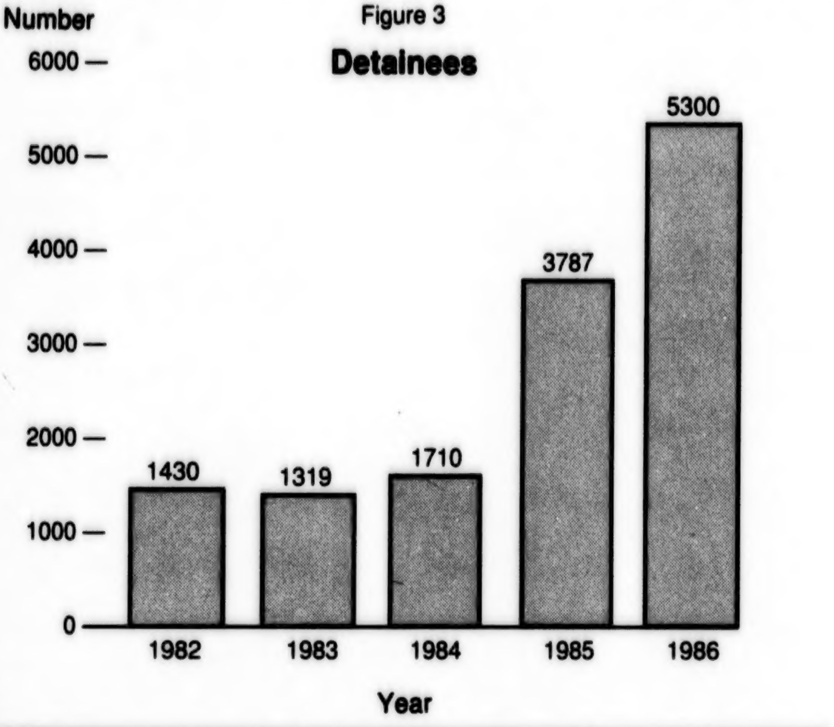


Figure 3



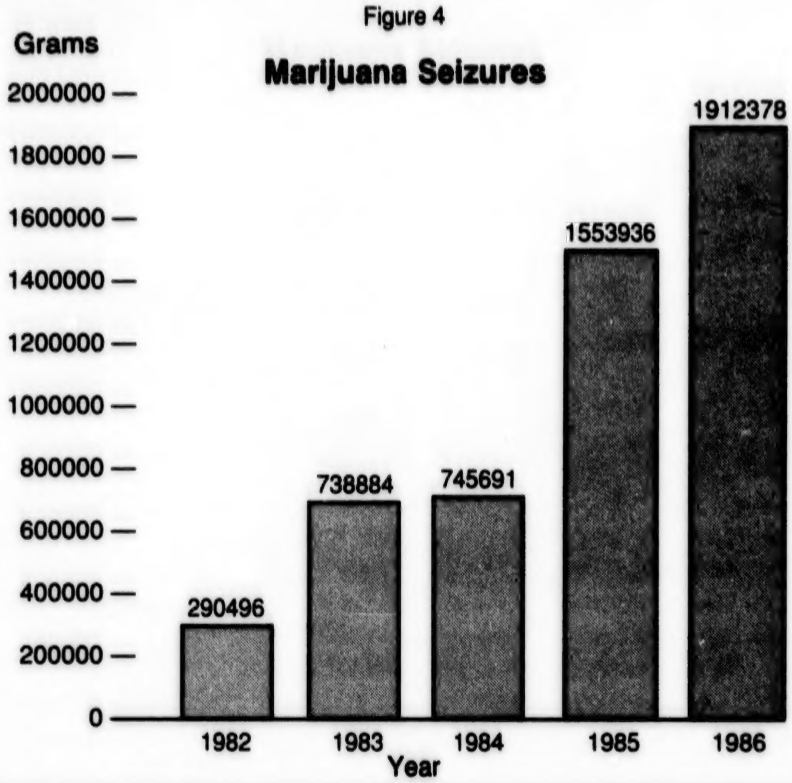


Figure 4

Marijuana Seizures

greater efficiency of the security forces, partly due to an improvement in facilities and specialized training, (2) an intensification of the drug traffic, as a consequence of greater concentration, and an increase of traffickers in the area due to their shifting towards South America and its consumer centers.

Seizures of hashish have been decreasing since 1984 (Figure 6), being now sporadic. There is not much hashish drug traffic in Argentina. Security force statistics regarding seizures of psychotropic drugs, which are heavily used perhaps do not reflect the real situation because they are not included in the schedules of the penal law (Figure 7). Their real importance in the problem of drug abuse in Argentina can be seen in statistics from Intoxication Centers, Medical Emergency Services, Toxicological Analytical Centers, and the Laboratory on Toxicology and Legal Chemistry of the Forensic Medical Body of Federal Justice (Garcia Fernandez, 1985). This information reveals the importance of psychotropic drugs consumption, especially the benzodiazepine depressants. The following therapeutically used psychotropics are abused: diazepam, lorazepam, flunitrazepam, trioxifenidile, dextromethorphan, zipeprol, and barbituric acid derivatives.

Figure 5

Marijuana Plants

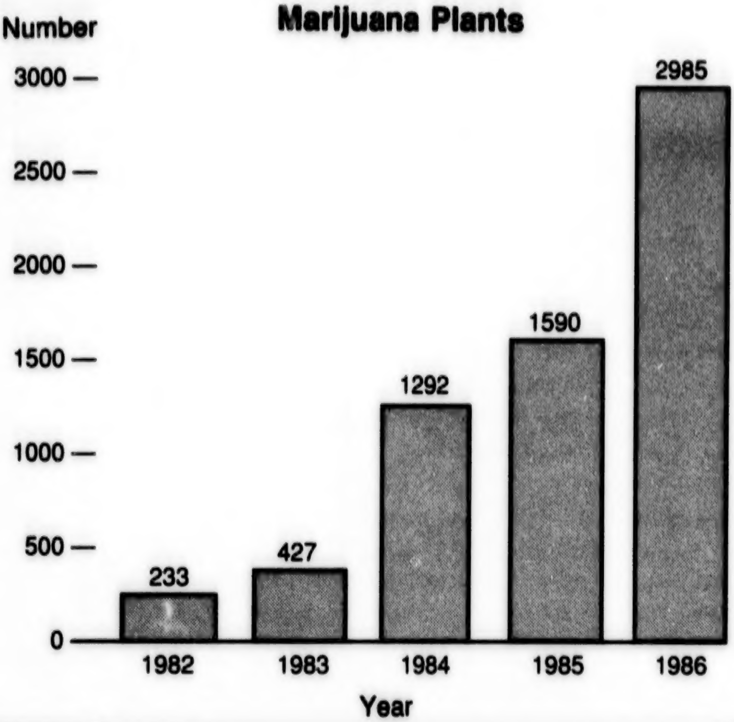
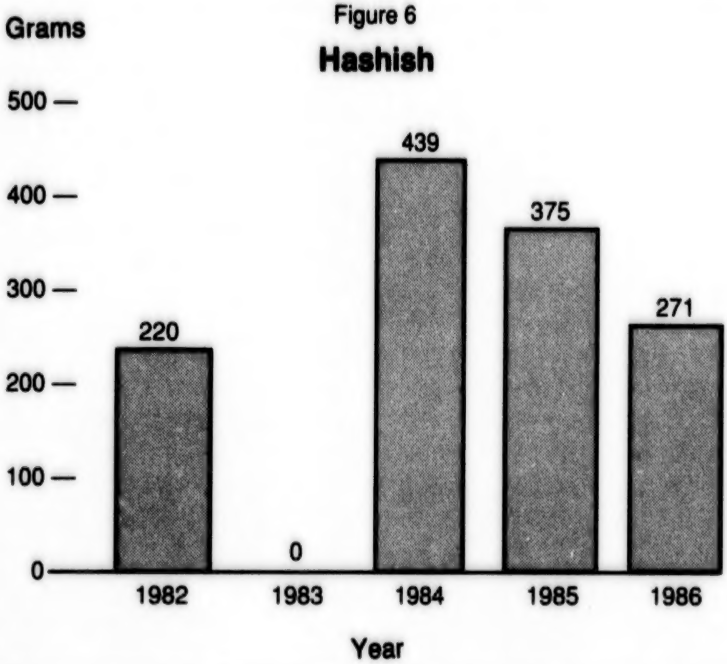


Figure 6

Hashish



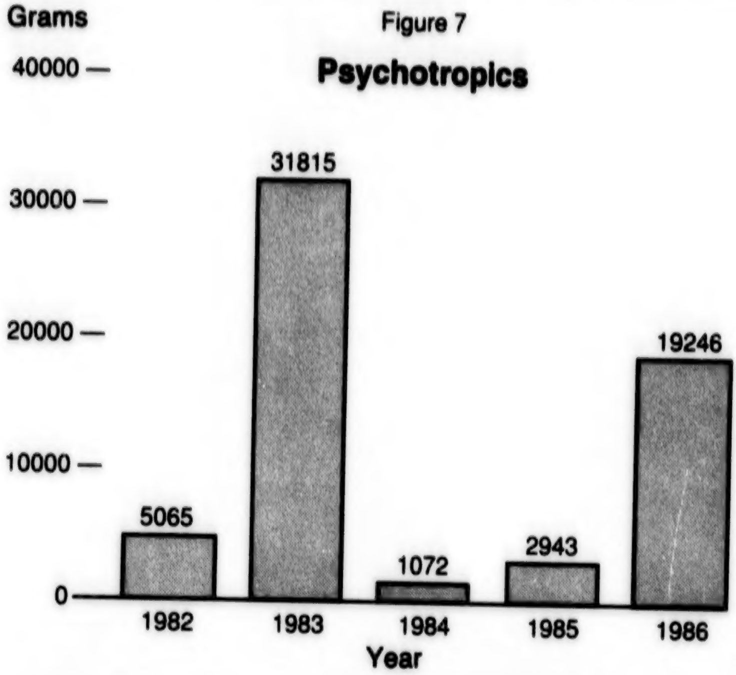


Figure 7

Psychotropics

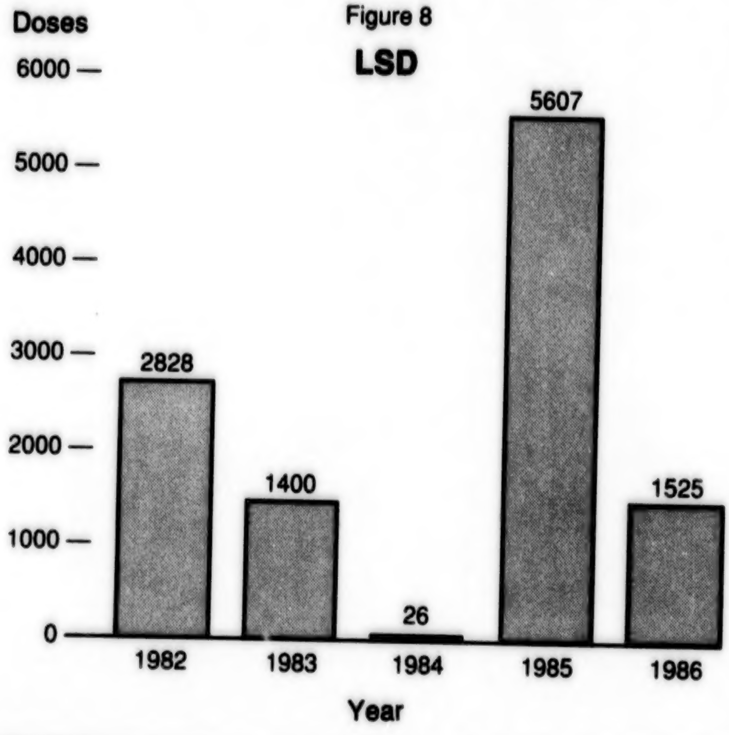
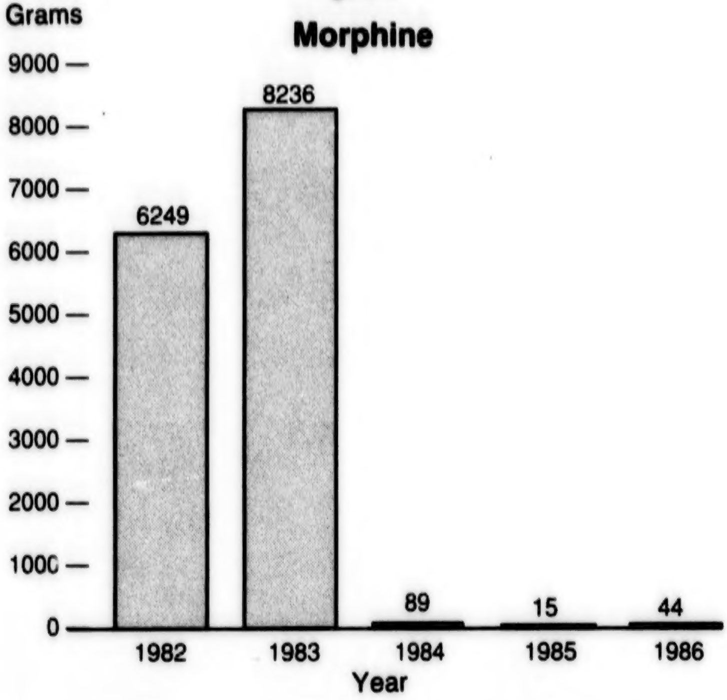


Figure 8

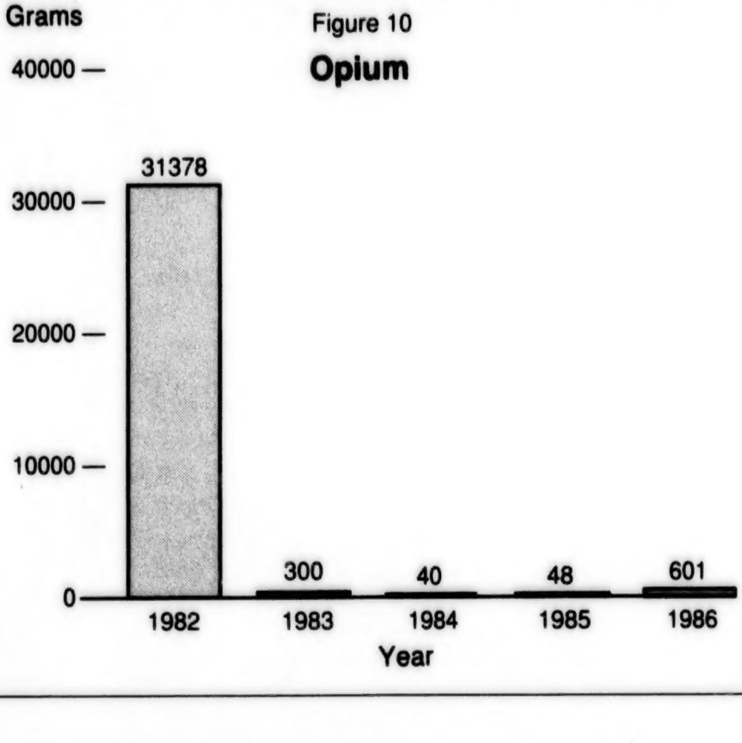
LSD

Figure 9



Morphine

Figure 10



Opium

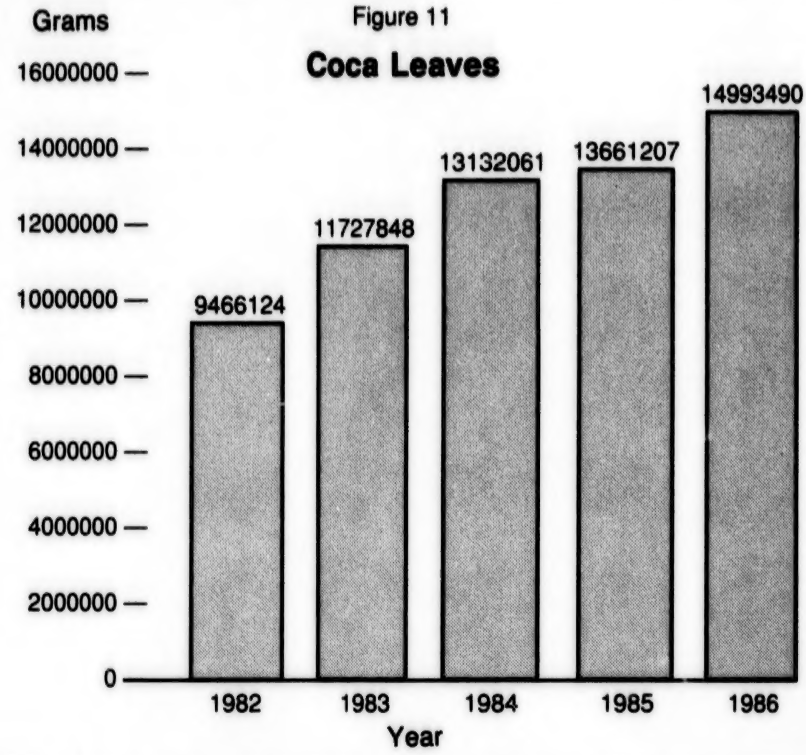


Figure 11

Coca Leaves

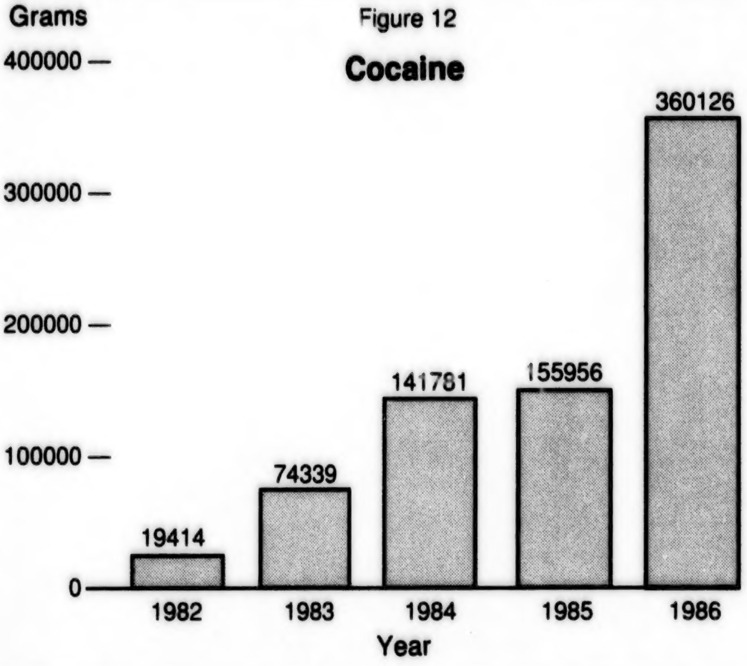


Figure 12

Cocaine

LSD seizures are seen occasionally (Figure 8), but currently LSD trafficking is a severe problem in Argentina. Likewise, there have been minimal seizures of morphine and opium in the last years, reflecting the minimal consumption of these substances in Argentina (Figure 9 and 10).

Coca leaf seizures have been low but consistent from 1982 to 1986 (Figure 11). One must remember the 25 year reservation made by Argentina as a Member of the Narcotic Convention of the United Nations (1961) to allow coca leaf chewing in those areas where it has been an established custom. New laws are being considered in Congress which may change the legal "status" of coca leaf chewing.

Cocaine seizures have increased tremendously between 1982 and 1986; the highest rate of increase was over 100 percent between 1985 (155,956 g) and 1986 (360,126 g) (Figure 12). Coca enters Argentina through the Northwest Frontier (Salta and Jujuy Provinces) which borders Bolivia. Drug traffic has become an even more serious control problem since Argentina, which was once only a drug transiting country has become a country where traffic and consumption exist.

Precursor, Essential and Reagent Chemical Control

At this time, control of essential chemicals in Argentina is limited to those chemicals used in the production of cocaine hydrochloride. These substances are smuggled into Bolivia where their sale is restricted.

This problem was first noticed in June, 1982 when the Regiment "Oran" from the National Frontier Police (Gendarméria Nacional) informed the Ministry of Health that local people from various businesses bought great quantities of chemical products that were smuggled into Bolivia (hydrochloric acid, sulfuric acid, ethyl ether, formaldehyde, acetone, borax, sodium bicarbonate, ammonia water, etc.). The packaging was changed and the chemicals were put into cooking oil bottles or flour bags, and under the regime of "neighbor frontier traffic," they crossed the border. At other times the products were smuggled at night where no border guards were located. This was the reason why federal representatives asked for Executive Power to adopt "more energetic and effective" measures to prevent the uncontrolled sale of several of these substances.

After the province of Salta adopted such control measures, the Federal Government passed National Resolution Number 365 (November 12, 1986) for the control of the importation and exportation of chemical substances which were listed in Annex "A" (precursors) and Annex "B" (essential chemical products) of the resolution.

Annex "A" includes: rye ergot, phenyl-2-propanone, phenylacetic acid, anthranilic acid, N-acetylanthranilic acid, piperidine, ergotamine and its salts, ergonovine, and norpseudoephedrine which are precursors for the production of amphetamines, phencyclidine, LSD, and methaqualone.

Annex "B" includes: ethyl alcohol, petroleum ether, kerosene, hydrochloric acid (concentrated and dilute), sulfuric acid, sulfur trioxide, ammonia, ammonium hydroxide, sodium and potassium hydroxides, sodium sulfate, sodium carbonate, potassium carbonate, potassium permanganate, benzene, xylene, chloroform, methyl alcohol, ethyl ether, acetone and methyl ethyl ketone (Decreto Nacional No. 365, 1986).

The abuse of volatile solvents by inhalation was first reported in 1968. In 1975 the known cases of the Neuropsychiatric Borda Hospital Buenos Aires and of the Treatment and Rehabilitation Center (CENARESO) were reviewed. This review included a description of organic solvents used as drugs of abuse. The abuse of solvents and glues increased in 1981–1982. The chief substances were adhesives and glues that contain toluene as the solvent, naphtha, aerosol pharmaceutical products with freon, which have caused several deaths, butane and industrial solvents, the most dangerous of which is benzene.

The situation has become so serious both in Buenos Aires and in the Provinces that currently Congress is considering three proposals whose aim is to control the sale of adhesives and glues that contain solvents or volatile organic compounds as diluting substances. These three proposals have been integrated into one which prohibits the use of benzene in the above mentioned products, limits its sale to people under 16, requires them to be labeled as "highly toxic" products and impose taxes on those who violate the rules.

Recently, Commandant Esquivel (from the Gendarmeria Nacional) said: "Argentina continues to be a transit country, in different ways, but, perhaps as it had been foreseen, with an increase in the use of drugs in permanent form."

Important centers were detected in Misiones, Neuquen, Cordoba, El Bolson, Bariloche and San Martin de los Andes. In these last patagonic areas, marihuana cultivation is carried out, even in small flower-pots, with the benefit of a special microclimate.

Although coca-chewing is now forbidden in Argentina, it is well known that in an area of approximately 292,000 square km. (Jujuy, Salta, Catamarca, Tucumán and Formosa), 180,000 people usually do it, specially at the sugar works.

It is characteristic of very poor areas. It is a problem not only of drug dependence, but of a serious social and economic condition, to which other problems such as alcoholism and tuberculosis may be added.

Since the magnitude of the problem of home consumption of drugs is not easily measured, at least in our media, the best parameter to appreciate it quantitatively, is narcotraffic. For example: seizures of cocaine in 1984 reached 13 kilograms; in 1985, 62 kg., in 1986, 110 kg. and in the first six months of 1987, 70 kilograms (Data from Federal Frontier Police only).

Coca leaf seizures: in 1984, 10,923 kg.; in 1985, 13,775 kg.; in 1986, 17,814 kg.; and in the early 1987, 70 kg. They enter Argentina through La Quiaca, Aguas Blancas and Professor Salvador Mazza.

Buenos Aires is the starting point of the traffic towards Europe and the United States because its airport is the most important in this part of the continent. From Santa Cruz de la Sierra (Bolivia) the first step is Jujuy, by plane, and then by land to Buenos Aires.

Marijuana production is about a ton per hectare, with two annual crops. It is cultivated in Patagonia, very far from the northern frontier, for several reasons; one of them is because several years ago "hippy" groups established there; another is because in Chile marijuana is legal for textile use. The rest of it comes to Argentina by illegal traffic. The area of great production of marijuana in Chile is Ayacucho (Mendoza Argentina).

A new law on narcotics is presently being considered by the Federal Penal Legislation Commission of the Lower House (Ordinary Sessions, 1986; Day Order No. 691). The legislation deals with "Narcotics, Legal Prevention, Regulations for their production, fabrication, sale and their use." This project was approved with modifications by the Federal Senate, and is on revision by the House of Representatives. Many punishable situations are considered in detail; sowing or cultivating of plants to produce narcotics, production, preparation, commerce, distribution and traffic, when for profit; introduction into and dispatch from the country. The law establishes the situations in which penalties must be increased.

An important modification of this law reduces the penalty in cases of small quantities for personal use.

In those traditional areas of coca leaf chewing, the Magistrate will be able, according to circumstances of the case, to eliminate or reduce the penalty to a minimum.

In cases of dependence, treatment or detoxification and rehabilitation programs in adequate centers will be indicated.

Conclusion

Although the drug abuse situation in Argentina has not reached the serious level known in other parts of the world, it is serious enough to bring about the adoption of urgent measures to enforce strict control of the situation involving increased drug traffic.

References

Cattani, H.R., "Legislation Sobre Estupefacientes y Psicotropics de la Republica Argentina", 1977, Artes Gráficas Negri S.R.L. Buenos Aires, Republica Argentina.

Informe sobre la Red de Informatica. Dr. Jośe Corsunsky, Asesor del Vice Presidente Ejecutivo, de la Comisión Nacional Contra el Narcotráfico y el Abuso de Drogas.

Resolucion no. 129, Ministerio de Salud y Acción Social, 6 de Febrero de 1987.

Información del Banco de Datos de Policía Federal, en base a antecedentes suministradospor todas las Fuerzas de Seguridad (1987).

Información suministrada a la Comisión Contra el Narcotráfico y el Abuso de Drogas por la Dirección Nacional de Adunas (1987).

Garcia Fernandez, J.C.—Informe presentado a WHO (1985) No. publicado.

Cattani, H.—Informe a la Comisión Nacional contra el Narcotŕafico y el Abuso de Drogas. "Precursores, Productos Quimicos Esenciales Y Reactivos."

Decreto Nacional No. 365 (13/III/86). Publicado en el Boletín Oficial dela 18/III/86.

Garcia Fernandex J.C., Equipo Para la Investigacion Rapida de Drogas de Abuso." Presentado a la Reunion de Expertos de Naciones Unidas sobre Metodología Analítica para Drogas de Abuso, Revisión y Acutalización (Viena, Austria, Mayo 25/1987).

Concerns of Industry

Margaret Cone

The International Federation of Pharmaceutical Manufacturers Association (IFPMA), through Member Associations in 51 countries, represents the manufacturers of prescription medicines in the developed and developing world. For several years IFPMA has been actively involved with the World Health Organization's (WHO)'s review of psychoactive substances, for possible scheduling under the international drug control conventions, where this action has involved drug substances with a therapeutic use in marketed products. The position of the pharmaceutical industry, with regard to regulation of medicines and legislation on controlled substances is by no means a negative one. The industry recognizes and supports the need for, and usefulness of well founded, equitable national controls over the manufacture, distribution and sale of medicinal products. Concern has, however, arisen in connection with the implementation of the international conventions in recent years. The first concern is that the efficiency and effectiveness of the treaties may be undermined by the inclusion of large numbers of therapeutic substances for which there is little evidence of a serious global problem. Industry believes that there are examples of this to be found in recent scheduling decisions. A second major concern is for the patient, the legitimate consumer of the psychoactive medicines which come under international control. Countries in the Third World, without the infrastructure to handle basic regulation of medicines (prescription-only restrictions, control of retail outlets, etc.) may apply unduly stringent controls in the case of narcotics—which can have serious effects on the access and availability of essential medicines to the patients who depend on them.

Although legislation on controlled substances may stimulate the development and proliferation of analogues by the illicit manufacturer there is concern that the same legislation may act as a deterrent to the research and development of new psychoactive medicines by the legitimate industry. Of particular concern is the development of substances for the treatment of drug addicts or for alleviation of symptoms of withdrawal since, by using such drugs in an abuser population there is a high probability that the substances themselves will come under suspicion and be subject to the review procedure.

There are, however, important areas for cooperation between industry and the international agencies in the field of information exchange and evaluation of data on instances of reported abuse of medicinal drugs. Every effort should be made to promote such cooperation and to foster greater confidence in both parties.

The prospect of additional controls on precursors, solvents, and reagents are of obvious concern to companies whose manufacturing operations depend on such substances and extensive consultation between industry and regulatory bodies is obviously essential.

The establishment of priorities, on a rational basis, and the mutual recognition of the problems of both parties—the regulated and the regulators—should improve the prospects of finding a workable solution to the emerging threat posed by the illicit analogue manufacturers.

The Problem of Analogues vs International Drug Treaties

Dr. István Bayer

The problem of analogues of drugs of abuse is not new. It is demonstrated by examples of how problems could be solved by international instruments under various conditions and in different periods of time. Possibilities were offered by the Single Convention on Narcotic Drugs, 1961 for the solution of current problems but these possibilities were hindered by the existence of the Convention on Psychotropic Substances, 1971. The 1971 Convention does not allow the direct application of the similarity concept for the scheduling of substances and this obstacle cannot be removed without amending that Convention. Such an amendment to the 1971 Convention can be suggested but passage would be a lengthy process. Therefore, an immediate course of action is suggested through a resolution by the Commission on Narcotic Drugs.

The fifteenth Norman Kerr memorial lecture of the Society for the Study of Inebriety was delivered by Sir Malcolm Delevingne on October 2, 1934 at Friends' House, Euston Road, London, on "Some international aspects of the problem of drug addiction." Sir Malcolm, the British representative in the Opium Advisory Committee in the League of Nations presented an excellent overview of the international drug problems of the 1920's and 1930's and the description of the development of the international drug control system. The greatest international problem of this period was the unlimited manufacture of opiates (first of all morphine and heroin) by European firms who were engaged in the illicit traffic on a big scale. This situation was clearly described by Sir Malcolm who added the following remarks (Delevingne, 1935):

". . . One device which was operated with success, and on a large scale by such firms was the conversion of morphine into one or other of its esters—in particular, benzoyl morphine—from which the morphine could be recovered without difficulty or which could themselves serve as drugs of addiction. These esters were not covered by the terms of either the Hague Convention or the 1925 Convention. In 1928, when the facts came to light, the Advisory Committee recommended that Government should apply the system of control to benzoyl morphine, and by 1930 most Governments had done so. This omission has now been made good by the Convention of 1931."

The term of "large scale" is justified because:

". . . In the careful analysis which was made for the International Conference of 1931 by the Opium Section of the League Secretariat—an analysis based on the returns made to the League by Governments—it was estimated that during the six years (1925 to 1930), no less than 72 tons of morphine in various forms escaped into the illicit traffic."

During the 1940's new potent analgesics were marketed in Germany. Pethidine (meperidine) was the first, and was followed very soon by methadone. It is not by chance that one of the countries where the development of these new compounds took place was Germany. Germany was the birthplace of chemistry and the chemical and pharmaceutical industries and a leading country in drug research. Additionally, there were memories of World War I when Germany had great difficulties with the procurement of opium for morphine manufacture. Their systematic research had two aims: to develop synthetic compounds with morphine-like analgesic activity which did not produce dependence and to assure the supply to the army without opium during the war in prospect.

It has become evident that the new compounds do have abuse and dependence potential and synthetic narcotic analgesics were put under international control by the 1948 Paris Protocol. It is a well known fact that the process of scheduling synthetic narcotic analgesics is still going on.

The case of morphine esters and the example of synthetic narcotic analgesics illustrate the existence of the problem of "analogues" many decades ago, and the study of the 1961 Convention reveals the awareness and concern of its drafters, as follows:

1. Some people believe that the scheduling of a drug under the 1961 Convention means the control of a specific compound and its preparations only, and there is no place for a decision on a group of drugs. This is only partially true because the control of a drug under Schedule I means the *automatic* control of its isomers, esters and ethers, and salts of all of these derivatives. The scope of Schedule II is more limited; the automatic control applies only to isomers and salts, in that esters and ethers are not covered. There are possibilities for the exemption of a derivative from Schedule I control measures. One way is to place such a derivative into Schedule II (for example, codeine). It is possible to exempt a drug completely from the narcotics control regime: Schedule I contains a statement that dextromethorphan and dextrorphan (optical isomers of the respective levo-compounds in the Schedule) are specifically excluded. But the flexibility of the 1961 Convention can be best illustrated by the example of ecgonine. This cocaine precursor has been scheduled with the following wording: "Ecgonine, its esters and derivatives which are convertible to ecgonine and cocaine."

The importance of this provision lies in the fact that it controls all of the ecgonine derivatives but, at the same time, exempts such derivatives which are not convertible to ecgonine and cocaine. This is a good example of the scheduling of a class of chemical compounds without listing their names, and, future compounds which do not exist at present as well.

2. The scheduling concept of the 1961 Convention is based on similarity of effects and abuse potential and authority has been given to the

World Health Organization (WHO) for the establishment of this similarity. Article 3 of the Convention defines very clearly the decision making procedure: "If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission . . ." The Commission may accept or reject this recommendation but has no right to alter it.

In the light of the above mentioned examples, possibilities are offered by the 1961 Convention for the prompt or even preventive scheduling of groups of analogues. For example, in theory at least, it would be possible to follow the ecgonine model and put fentanyl *derivatives* into Schedule I. If the exemption of any specific derivative would be necessary it could be mentioned by name, following the dextromethorphan model.

Unfortunately, the functioning of the 1961 Convention and the use of the similarity concept were disrupted by development of the 1971 Convention. The reasons are clearly described by the late Dr. Lande, who was the drafter of both Conventions, as follows: "It has been admitted by officials of the World Health Organization in meetings as well as in discussions with the writer of this paper that the ill effects of amphetamines could for the purpose of applying Article 3, Paragraph 3, Sub-Paragraph (iii) be considered "similar" to those of cocaine, both causing central nervous system stimulation." They have equally asserted that the ill effect of barbiturates which are addiction producing and of those tranquilizers which are also addiction producing could also for this purpose be considered to be similar to the ill-effects of morphine, all of these drugs producing central nervous system depression. The reason why the World Health Organization cannot assume this similarity is not necessarily *technical* but *legal*: The Office of Legal Affairs of the United Nations ruled, in an opinion given to the Commission on Narcotic Drugs at its twenty-third session that barbiturates, tranquilizers and amphetamines were outside the scope of the Single Convention. The Office based this opinion on the consideration that there was an understanding at all stages of the drafting of the Single Convention and in particular also at the Conference of 1961 which adopted the Single Convention that this treaty should not be applicable to these three types of substances although the effects of the amphetamines have some degree of similarity to cocaine and those of barbiturates and some tranquilizers to morphine. It may be added that this understanding was reached at the 1961 Conference particularly at the insistence of the U.S.A. delegation. This delegation was obviously motivated by the opinion that the huge burden which would be placed on international and national control organs by subjecting amphetamines, barbiturates and tranquilizers to the narcotics regime would fatally weaken this regime in the campaign against addiction to narcotic drugs and thus frustrate international efforts which have been made for more than half a century.

The 1971 Convention is the result of this "understanding" and the concept of similarity was replaced by artificial scheduling criteria and the lack of WHO authority has been later substituted by a complicated multistage evaluation mechanism.

The purpose of this paper is not the description of the weaknesses of the 1971 Convention but it was necessary to draw the attention to two basic issues: (1) the incompatibility of the two Conventions, and (2) the counter productivity of the 1971 Convention by hindering such actions which would be possible under the 1961 Convention (including the scheduling of precursors).

I do not think that this Conference could speculate about amending the 1971 Convention or about its merger with the 1961 Convention, but could recommend such an action as a long-term goal. For the time being it can be suggested that the Commission on Narcotic Drugs (CND) should issue a resolution requesting Governments:

A. To adopt legislative measures against the unauthorized manufacture, sale and distribution of analogues of controlled psychoactive substances (i.e., narcotic drugs, psychotropic substances and other similar drugs under national control),

B. To inform the Secretary-General about such legislative measures and their experiences, and

C. In the case of analogues of narcotic drugs, to notify the Secretary-General for the amendment of the Schedules of the 1961 Convention, in conformity with Article 3, Paragraph 1.

Author Index

Bain, Ian, 21
Bayer, Istvan, 319
Brine, George A., 67
Cami, Jordi, 147
Carroll, F. Ivy, 67
Cima, L., 207
Cone, Margaret, 317
Cooper, Donald A., 95
Fazli, F. R. Yousuf, 273
Ferrara, S. David, 207
Finnegan, Kevin T., 195
Garcia Fernandez, Juan Carlos, 301
Glennon, Richard A., 39
Haislip, Gene R., 3, 291
Henderson, Gary L., 7
Kelemen, K., 135
Keup, Wolfram, 239
Khan, Inayat, 1
Klein, Michael, 175
Kouidri, Cherif M., 29
Lehmann, Pedro A., 117
Luisada, Paul V., 233
Malliori, Meni, 283
McKinnon, Raymond J., 285
Poshychinda, Vichai, 257
Scaplehorn, A. W., 91, 295
Schuster, Charles R., 195
Tollenaere, Jan P., 125
Woodworth, Terrance W., 21
Yanagita, Tomoji, 161

BLANK PAGE

Subject Index

Abstinence syndrome, 135-136
Abuse liability, 137
Abuse liability, assessment of, 161, 162-170
Abuse liability, prediction of, 170
Acetylating agents, 110, 112
Agonist, 138
Agonist-antagonist (mixed), 138
Alcohol, 137, 151-155
Amination of phenylpropanones, 39-40, 40-41
Amphetamine analogues, synthesis of, 38-55
Amphetamine analogues, stimulus properties of, 56-65
Amphetamine(s), 21-22, 24-25, 139-141
Amphetamine(s), CNS effects, miscellaneous effects, mortality, 219-225
Amphetamine(s), impurities of, 179-185
Analytical methodology, 2, 10-11
Annual National Statistical Report, 23
Antagonist, 138
Argentina, drug laws and enforcement, 301-314
Arylcyclohexylamines. *See* Phencyclidine
Autonomic nervous system, 209

Barbier process, 104
Benzaldehydes, as precursors, 42-43
Benzenes, substituted, as precursors, 44-47
Benzoic acids, as precursors, 43, 47
Benzyl alcohols, as precursors, 43, 46-47
Benzyl halides, as precursors, 43, 47
Bundeskriminalamt, 21, 252
Buprenorphine, 245-248

California experience, 7
Cannabinoids, 137, 151, 153-154
Cannabis, 147-148
Cataleptic anaesthetic, 233
Cardiovascular system, 209
Central Information System on Drug Abuse Problems, xvii
Chemical Diversion and Trafficking Act, 291, 294
"Chemical Signature", 27, 175
"China White", 7
CNS depressants, 137, 143
CNS effects, 172, 207-209
Coca leaf, 95-96
Coca paste isolation, 96-97
Cocaine, 147-149
Cocaine, abuse, 249-252
Cocaine, base, 97-98
Cocaine, hydrochloride salt, 98
Cocaine, impurities, alkaloidal, 99-100, 178
Cocaine, impurities, chemical processing, 100-101
Cocaine, production, 95-101
Cocaine, production, chemicals, 99, 229
Cocaine, synthesis of, 98-99
Comprehensive Multi-Disciplinary Outline (CMO) or Document, related to ICDAIT, 2
Continuous self-administration experiments, 164-165
Controlled substance analogue (designer drug), definition of, xiii
Controlled Substance Analogue Enforcement Act, 291
Convention on Psychotropic Substances-1971, xvii, 21, 35, 161, 296-297, 291-292, 301-303, 319-322
"Crack" cocaine, 156
Cross physical dependence experiments, 168-169
Cross self-administration experiments, 164
Cross-dependence, 136
Cross-tolerance, 136
Customs and Excise Management Act 1979, 296-297
Cyclic N-substituted phenalkylamines, 54-55, 56

Data, on pharmacological effects and public health problems, 2
Demand reduction, 257, 272, 302
Dependence, 207
Dependence, physical, 135-136
Dependence potential, 150, 161-174
Dependence potential, physical, 165, 172
Dependence, psychic, 162, 165
Designer drug, xiii-xv, xxi, 5, 17, 18, 27, 250-252, 278-280. *See also* Controlled substance analogue.

Developing countries, 273-281, 301-316
3,3-Diphenylpropylamines, 129
Dissociative anesthetic, 142-143
Dopamine, 195
Drug abuse, 136-137, 207
Drug abuse, National Survey on, Pakistan, 275, 281
Drug abuse, prevention, 302
Drug abuse and trafficking, evolutionary concepts of, 3-6
Drug abuse and trafficking, historical development of, 3-6
Drug dependence, definition of, 162
Drug dependence, Thailand data base on, 257
Drug discrimination studies, 39, 57-61, 166-167, 197-198
Drug interactions, 211-213
Drug trafficking statistics, 23-27
Drugs Trafficking Offenses Act 1986, 296, 298

Early Warning System, xvii
ECD, 11
Electron capture detection, 11
Emergency scheduling, xvii, 291
Epidemiological data, 16-17, 239-242, 261-272, 283-284
Essential chemical, control of, 313-315
Essential chemical, definition of, 281
Essential chemicals, illicit trade of, 26-27
Etonitazene, 132
Expert Group meeting, WHO, xiv, xv, 33-34

Federal German Office of Criminal Investigation, 252
Fentanyl and fentanyl analogues, 7, 67-90, 130-131, 149,
  CNS effects, miscellaneous effects, mortality, 225-227
  Methods of analysis, 10-11
Fires and explosions, as investigative leads, 289

Gas chromatography, 11
Gases, abuse liability of, 137
GC, 11
GC-ECD, 11
Generalization, definition of, 166-167
Generalization, stimulus, 39, 51-53, 57, 60-61
  Amphetamine-like, 56-61, 141
  DOM-like 56-61, 141
Glue, abuse liability of, 137
Government agency-regular records, 258-261
Greece, abuse of illicit substances in, 283-284

Hallucinogens, CNS effects, miscellaneous effects, mortality, 212-219
Hallucinogens, SAR, 117, 120-123, 142, 143
Harm liability, 161, 170-173
Heads of National Narcotics Law Enforcement Agencies (HONLEA), 34
Heroin, 95-112, 147-148
Heroin, impurities, 108-111, 176-178
Heroin, impurities, acidic, 109-110, 111
Heroin, impurities, alkaloidal, 108-109
Heroin, impurities, neutral, 109-110, 111
Heroin, production, chemicals, 108, 230
Heroin, production, from codeine, 25, 107-108
Heroin, production, from morphine, 101-112
Heroin, production, from total synthesis, 108
Heumann process, 104
5-HIAA, 199, 203
Human reproductive system, injuries of, 211
5-Hydroxyindoleacetic acid, 199, 203

ICDAIT, 2
IFPMA, 317
Ill effects, assessment of, 170-171
Ill effects, prediction of, 172-173
Illicit drug trafficking, 23-27
Immediate precursors, scheduling of, 294
Immune system, injuries of, 211
Impurities, 175-190
Impurities, processing, cocaine, 229
Impurities, processing, heroin, 230
Informants, as investigative leads, 288
Inhalants, abuse liability of, 137
International Collection of Reference Substances, xiv, xviii, 1
International Conference on Drug Abuse and Illicit Trafficking (ICDAIT), 2
International drug abuse control strategy, 34
International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 317
INTERPOL, xiv, xvii, 1, 21-27
Intervention technology, 272
Investigative techniques, 285-290

Ketobemidone family, 67, 70-72
Kidney, injury to, 210-211
Knoevenagel reaction, 39-40, 41-48

Law Reform (Miscellaneous Provisions) (Scotland) Act 1985, 297-298
Lead poisoning, 182-185
Leadership Conference on Controlled Substance Analogues, (DEA), xiv
Leuckart reaction, 40-41, 91
Liver, injury to, 209-210
LSD, illicit synthesis of, 92-93
LSD, trafficking in, 22, 25
Lysergic acid diethylamide. *See* LSD
Lysergide. *See* LSD

Manual, working tools, 31-32
Mass spectrometry, 11
MDA, xiii, xv, 5, 41, 50-54, 57, 60-61, 121-122, 141, 147, 196-203, 213, 252-255, 282
MDE, 61, 201
MDMA, 6, 41, 50-53, 60-61, 121-122, 147, 196-203, 252-255, 282
Medicines Act 1968, 295-297
Meperidine, xv, 21, 68-69, 129
Meperidine family, 67, 68-70
Meperidine, analogues, CNS effects, miscellaneous effects, mortality, 225-227
Methamphetamine, 22, 25, 26, 27
Methamphetamine, illicit synthesis, 179-185
Methamphetamine, impurities in, 179-185
Methaqualone, 24, 26
Methaqualone, CNS effects, miscellaneous effects, mortality, 227-229
Methaqualone, illicit synthesis, 93, 188
Methaqualone, impurities in, 179-185, 188-189
Methaqualone analogues, illicit synthesis, 188-189
4-Methylaminorex, xv, 54-55
Methylenedioxy amphetamines, 195-203
3,4-Methylenedioxyamphetamine. *See* MDA
3,4-Methylenedioxymethamphetamine. *See* MDMA
3,4-Methylenedioxyethylamphetamine. *See* MDE
3,4-Methylenedioxy-N-hydroxyamphetamine. *See* N-OH MDA
1-Methyl-4-phenyl-4-propionoxypiperidine. *See* MPPP
1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *See* MPTP
"Me-too" drugs, 147-149, 156-157
Misuse of Drugs Act of 1971, 295-297
Mixed agonist-antagonist, 138
"Modified jumping test", 143-144
Monitoring systems of specific populations, 261-272
  Army and Navy recruits, 261, 270
  Drug dependent treatment population, 261, 261-268, 269-270
  Secondary school students, 261, 268-270
Morphine, effects, 139
Morphine, isolation, purification, 102-106
Morphinomimetics, 125-126
MPPP, xv, 22, 73, 178-179, 214, 216, 225-227
MPTP, 73, 178-179, 214, 216, 226-227
MS, 11
Multilingual Dictionary of Narcotic Drugs and Psychotropic Substances Under International Control, 34

N-alkyl phenalkylamines, 50, 54
National Central Bureaus (NCB), 21
National laboratories, establishment and/or strengthening, 30-31
NCB, 21
Neurotoxicity, 195-203
Neurotransmitters, 117-118, 195
N-hydroxy phenalkylamines, 54
Nicotine, 137
N-OH MDA, 61
Norepinephrine, 195
N-substituted phenalkylamines, synthesis, 50, 54, 55

OIPC-INTERPOL, 21-27
Opioids, 137-140
Opium poppy, 95, 101-104
Overdose deaths, 7, 12

Pakistan, drug abuse problem in, 273-281
PCP. *See* Phencyclidine
PEPAP, xv, 73, 214, 216, 225-226
Pharmacokinetics, 156
Pharmacology, clinical, 147-160
Pharmacology, preclinical, 135-145
Pharmacophore, definition of, 125
Phenalkylamines, as precursors, 47-48, 48-50
Phencyclidine, 91-92, 142-143, 233-237
Phencyclidine, illicit synthesis, 91-92
Phencyclidine, impurities in, 185-188

Phencyclidine analogues, illicit synthesis of, 91-92
Phenethylamine, 39
1-Phenethyl-4-phenyl-4-acetoxypiperidine. *See* PEPAP
Phenols, as precursors, 44, 47
4-Phenylpiperidines, 67-90
4-Phenylpiperidines, derivatives, 126-132
  Bicyclic structure, 129
  Hexacyclic structure, 127
  Pentacyclic structure, 126
  Tetracyclic structure, 127
  Tricyclic structure, 127-129
Phenylpropanone amination, 39-40, 40-41
Physical dependence, definition, 135
Physical dependence studies, humans, 169-170
Physical dependence-producing experiments, 169
"Piperidine Reporting", 293-294
Precursor chemical, control of, 313-315
Precursor chemical, definition of, 291
Precursors, illicit trade of, xiii, 26-27
Precursors, tracking of, 285-288
Prodine family, 67, 72-78
Program Planning Working Group (WHO/PPWG), xiv
Progressive ratio experiments, 166
Propiophenones, as precursors, 47-48
1972 Protocol Amending the Single Convention, 35
Psychic dependence, reinforcing effects, 167-168
Psychic dependence, subjective effects, 167
Psychic dependence potential, 171-172
Psychotropic Convention. *See* Convention on Psychotropic Substances-1971

Radioimmunoassay, 11
Rebound effects, 135-136
Receptor types, opioid, 138
Reinforcing efficacy (properties), 150, 166-168
Reference literature collection, 36-37
Reference samples of substances under international control, 35-36
RIA, 11
Robertson-Gregory Process, 102, 103-104

SAR, 57, 117, 119, 125
SAWS, 239, 242-255
Schwyzer process, 104
Self-administration experiments, 162-166
Self-destruction, 234
Serotonin, 195
Single Convention on Narcotic Drugs 1961, xv, xvii, 21, 35, 161, 296, 301-302, 319-322
"Similarity concept", 320-322
Solvents, abuse liability of, 137
Solvents, in cocaine samples, 100-101
Spain, drug abuse, 147-160
Spain, drug consumption, 147-148
Stimulants, SAR, 117, 119-120
Structure-activity relationships, 57, 117, 119, 125
Subjective effects, 150, 167
Substance Abuse Warning System. *See* SAWS
Substituted benzenes, as precursors, 44-47
Supply reduction, 302

Thailand data base on drug dependence and illicit drugs, 257
Thiboumery and Mohr Process, 102, 103
Threat assessment, xv
(+)-s-Tifluadom, 131
Tips, on clandestine laboratory activity, as investigative leads, 288
Tobacco, 137
Tolerance, 135, 165, 172, 207
Toxicity, acute, 172
Toxicity, behavioral, definition, 235
Toxicity, organ, 172, 207-230
Training of scientists, 29-30
Treatment and rehabilitation programs, 283-284

Undercover work, as investigative leads, 289
United Kingdom, misuse of drugs enforcement, 295-299
United Nations Commission on Narcotic Drugs (UN/CND), xiv, xv, xvii, 29-38, 161, 319-322
United Nations Division of Narcotic Drugs (UN/DND), xiv, xvii, xviii, 1, 29-38
United Nations Economic and Social Council (UN/ECOSOC), xvii, 34, 161
United Nations Fund for Drug Abuse Control (UNFDAC) xix, xxiv, xxvii, 2, 32-33, 281
United Nations General Assembly, 29, 34
United Nations Laboratory of the Division of Narcotic Drugs, 29-38

Urine testing, 270

Victims of drug use, as investigative leads, 288-289

WHO (World Health Organization), xiii, xiv, xvii, xviii, 1-2, 22-23, 161, 317, 320-322
WHO Expert Group, xiv, xv, 33-34
Withdrawal syndrome, 135-136

☆ U.S. GOVERNMENT PRINTING OFFICE : 1989 O - 237-720 : QL 3

END

5-12-93